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MULTIPLE SCLEROSIS

[DISSEMINATED SCLEROSIS]

ASSOCIATION FOR RESEARCH IN NERVOUS & MENTAL DISEASES

A Series of Investigations and Reports

Volumes Published:

VOL. I. [1920]—ACUTE EPIDEMIC ENCEPHALITIS
[LETHARGIC ENCEPHALITIS]

VOL. II. [1921]—MULTIPLE SCLEROSIS
[DISSEMINATED SCLEROSIS]

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VOLUME II [1921]

MULTIPLE SCLEROSIS

[DISSEMINATED SCLEROSIS]

PAUL B. HOEBER
67-69 EAST FIFTY-NINTH STREET
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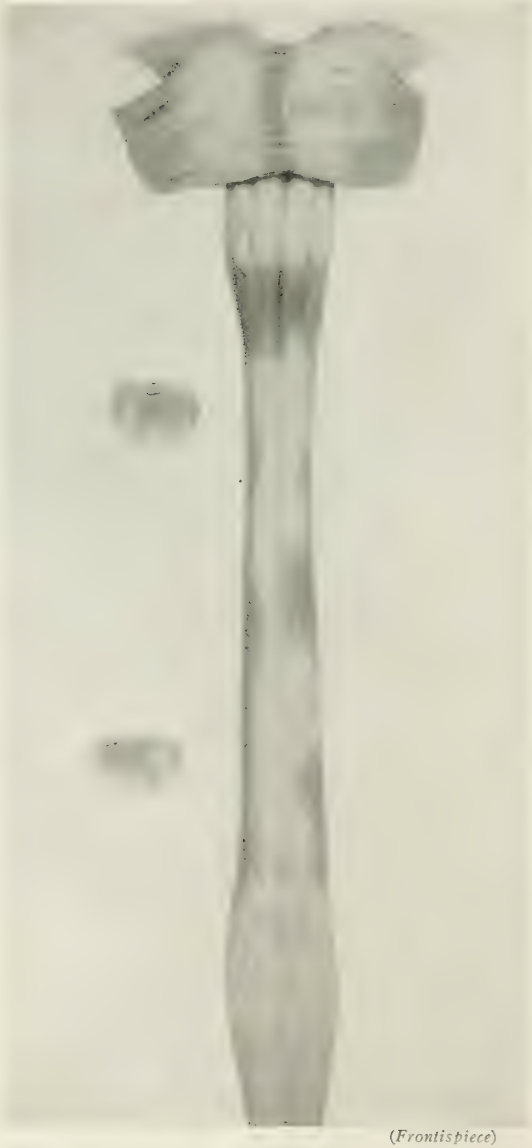

(*Frontispiece*)

The pathology of multiple sclerosis. From Pathologic Anatomy, by Robert Carswell, 1838.

MULTIPLE SCLEROSIS

[DISSEMINATED SCLEROSIS]

An Investigation by The Association for Research in Nervous and Mental Diseases

Report of the Papers and Discussions at the Meeting of the Association; New York City, December 27th and 28th, 1921

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ASSOCIATION FOR RESEARCH IN NERVOUS AND MENTAL DISEASES

LIST OF CONTRIBUTORS

Ayer, James B., M. D.
Instructor in Neurology and Assistant in Neuropathology, Harvard Medical School, Boston.

* Bailey, Pearce, M. D.

Barker, Lewellys F., M. D.
Professor of Clinical Medicine, Johns Hopkins University, Baltimore.

Brown, Sanger, 2nd, M. D.
Assistant Director of the Classification Clinic, Neurological Institute, New York;
Chairman of the State Commission for Mental Defectives, New York

Cadwalader, Williams B., M. D.
Associate in Neurology and Neuropathology, School of Medicine, University of Pennsylvania, Philadelphia.

Dana, Charles L., M. D.
Professor of Neurology, Cornell University Medical College, New York;
Visiting Physician, Bellevue Hospital, New York.

Davenport, Charles B., Ph. D.
Director of Biological Laboratory, Cold Spring Harbor, Long Island.

Davis, Thomas K., M. D.
Clinical Instructor in Medicine, Department of Neurology, Cornell University Medical College, New York.

Foster, Harold E., M. D.
Dalton Scholar and Assistant in Neurology, Massachusetts General Hospital, Boston;
Instructor in Neurology, Harvard Medical School, Boston.

Friedman, Emanuel D., M. D.
Adjunct Neurologist, Mt. Sinai Hospital, New York;
Adjunct Neurologist, Bellevue Hospital, New York.

Friesner, Isidore, M. D.
Otologist, Mt. Sinai Hospital, New York;
Assistant Aural Surgeon, Manhattan Eye and Ear Hospital, New York.

* Deceased.

Hassin, George B., M. D.
Associate Professor of Neurology, University of Illinois, College of Medicine, Chicago.
Holden, Ward A., M. D.
Professor of Clinical Ophthalmology, Columbia University, New York.
Jelliffe, Smith Ely, M. D.
Managing editor, *The Journal of Nervous and Mental Diseases*, New York.
Kraus, Walter M., M. D.
Clinical Instructor, Department of Neurology, Cornell University Medical College, New York.
Leiner, Joshua H., M. D.
Associate Attending Neurologist, Lebanon Hospital, New York.
McConnell, John W., M. D.
Associate Professor of Neurology, Graduate School of Medicine, University of Pennsylvania, Philadelphia.
Pardee, Irving H., M. D.
Instructor in Neurology, Columbia University, New York;
Associate Physician, Neurological Institute, New York.
Sachs, Bernard, M. D.
Neurologist, Mt. Sinai Hospital, New York;
Alienist and Neurologist, Bellevue Hospital, New York.
Spiller, William G., M. D.
Professor of Neurology, University of Pennsylvania, Philadelphia.
Strauss, Israel, M. D.
Associate Neurologist and Associate in Neuropathology, Mt. Sinai Hospital, New York.
Taylor, Edward W., M. D.
Professor of Neurology, Harvard Medical School, Boston;
Chief of Service, Neurological Department, Massachusetts General Hospital, Boston.
Teague, Oscar, M. D.
Timme, Walter, M. D.
Attending Neurologist, Neurological Institute, New York.
Wechsler, Israel S., M. D.
Associate in Neurology, Columbia University, New York.
Wilson, George H., M. D.

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PREFACE

The success of the volume on "Acute Epidemic Encephalitis" published by the Association in 1921 has been so complete, and the reviews have been so favorable, that the Editorial Committee has decided to follow unchanged the procedure of the preceding year. In view of the fact that the majority of the contributions have appeared in the current literature in full, the Committee has felt justified in using the papers according to its best interests and has freely edited them with the object of removing material not completely germane to the assigned title and of obviating repetition of essentially the same or very similar material. As pointed out in the preface to the volume on "Acute Epidemic Encephalitis" this has been done solely in the interest of unity in the publication and "not because of lack of excellence of any parts of the contributions received." At no time have any pertinent observations been elided. The discussions have been recorded essentially verbatim and only irrelevant and inconsequential matter has been omitted. Certain necessary editorial corrections, transpositions and rearrangements have been made, but the intent of the communication has been maintained.

The Editorial Committee desires to tender its thanks and appreciation to the individual contributors for their cooperation in rendering the preparation of this volume possible.

The prepared material was submitted to the President of the Association, who assigned the various sections to members of the Committee for editing. The conclusions of the Commission are presented at the close of each chapter.

Owing to the fact that no assignment concerning the differential diagnosis, course and treatment, was made prior to the meeting of the Association in December, these features were not reported upon at that meeting. To fill this gap, the President requested Dr. E. D. Friedman of New York City, to prepare a paper on this phase of the subject and it has been incorporated in the present volume.

The separate bibliographies have been removed from the individual articles and, in so far as was possible, have been added to the bibliography prepared by the Commission. The appended list of literature on the subject does not pretend to be complete, but it will be found reasonably satisfactory for anyone desiring to investigate the original sources of our knowledge of this disease.

H. A. R.

New York,
September, 1922.

CHAPTER I

General and Historical Considerations, Geographical and Racial Distribution, Incidence and Frequency, General Etiological Factors in Multiple Sclerosis, Exogenous Causes, Ecology and Conclusions

This first chapter deals in general with the known history of the disease, the geographical distribution of the disease and its incidence in the United States troops called under the draft law. The general statistics, the exogenous causes and the relationship of the disease to the social group are discussed.

The historical retrospect is written by Dr. Walter Timme of New York City.

The distribution of multiple sclerosis according to geographical and racial standards is discussed by Charles B. Davenport, Ph. D., of the Carnegie Institute of Washington D. C.

The incidence of multiple sclerosis in the United States troops is reported by Dr. Pearce Bailey of New York City.

The exogenous causes of multiple sclerosis are discussed by Dr. Lewellys F. Barker of Baltimore.

The statistics of multiple sclerosis have been collected and are presented by Dr. Israel S. Wechsler of New York City.

The consideration of multiple sclerosis in regard to the social unit and the methods of ecology is described by Dr. Charles L. Dana of New York City.

The conclusions of the Commission on the material presented are indicated at the end of the chapter.

Multiple Sclerosis—Historical Retrospect

Walter Timme, M. D.

A knowledge of the functions of the spinal cord existed even before the time of Galen in the third century. Indeed,

the ancients, exemplified by Hippocrates, used the term "paraplegia" as connoting a palsy of all parts of the body below the neck following an apoplexy. But Galen knew better than that,—he knew that there could be a partial paralysis depending not necessarily upon a cerebral apoplexy, but upon a disease or injury to any special vertebra as well. Thus, he thought that if the fifth cervical vertebra were injured or diseased the hands would be paralyzed, whereas if the sixth were affected, only a partial paralysis of the hands would ensue. His conclusions were derived from animal experimentation on monkeys to which the Greeks were given; and even more important and interesting is the fact that he derived this knowledge from his predecessors, Erasistratus, a grandson of Aristotle, and Herophilus of the Alexandrian School, who were permitted in that dark age to dissect the bodies of criminals and experiment upon them even during life. Vesalius in the sixteenth century decried this animal experimentation as demeaning to the human race and its conclusions as unwarranted in their application to man. So slight was the medical advance during the period of cloistered learning in the Middle Ages that the views of Galen held sway for eighteen centuries. Indeed, as late as 1819, John Cooke, delivering the Croonian Lectures in London on hemiplegia, paraplegia, paralysis partialis and epilepsy, depends for page after page of his address upon the findings and writings of Galen and the Greek School and quotes liberally from them to sustain his position!

The only new facts adduced by him in his lecture were those then recently advanced by the French School. That is to say, by Bichat, 1801, and Legallois, 1806–1810. Bichat divided the nervous system into two parts, the brain which was "animal," and the "ganglia" which were organic, i.e., they controlled the vegetative organs, digestion and so forth, and their activities were reciprocal, either one affecting and stimulating the other. Legallois showed that even though the cord were divided and all parts of the body below the division were paralyzed, that that did not necessarily prove that all life of the trunk depended upon the brain, a theory at that time commonly accepted, for in decerebrate pigeons and

rabbits with the vessels tied off, life in the trunk persisted for many hours if the lungs were kept inflated regularly with a blowpipe. He promulgated the principle that motion and sensation reside in the spinal marrow, which Galen had already known! Although this awakened no end of discussion, vitriolic in character, yet the French Institute declared for Legallois "that the principle which animates each part of the body resides in that portion of the spinal marrow from which the nerves of the part arise." Cooke further states that the paraplegia dependent upon a diseased state of the spine is by far the most frequent type of paralysis. It was produced mainly by mechanical injuries, falls and blows, and often in children, gradually following constitutional affections. But he did not differentiate the various special types as they were not "sufficiently interesting."

We then have an interim of fifteen years before the first differentiation of types of spinal paraplegia is made. Carswell, a medical student in London, following his masters about the hospital, requested and received permission to draw, in color, pathological tissues which were exhibited to the students. Among these sketches there appeared in 1837 one of the spinal cord with pons and medulla showing superficial colored plaques seemingly indiscriminately placed throughout the parts. This condition he described as "a peculiar diseased state of the cord and pons varolii accompanied by atrophy of the discolored portions, all of them occupying the medullary substance which was hard, semi-transparent and atrophied. It begins on the surface of the white and extends to the gray substance."

Almost contemporaneously, perhaps even as early as 1835, Cruveilhier described a similar condition pathologically as well as clinically. He calls the pathology a "gray degeneration" and states that it first shows itself in superficial taches which later attain a certain depth. This *sclérose en taches* or *en îles* appears at the expense of the normal white cord tissue which it replaces at times almost completely. "This new tissue is dense—much more so than the cord itself. I cannot compare this tissue with any other morbid tissue of which I have knowledge." He then describes a patient with the symptoms referable to such *sclérose en taches*. He

calls the condition "induration of the cord with paraplegia." As this is possibly the very first description of a case of multiple sclerosis appearing in the literature, and presented as such, it may be interesting to quote Cruveilhier verbatim. The patient was a woman, fifty-four years of age, who had been at the Salpétrière for at least ten years, and who had had the disease many years previous to her admission. "There seems to be a very incomplete controlling power of the will over the muscles which seem to obey imperiously some involuntary cause; and this conflict between the will and some involuntary cause produces incoordinate movements similar to those seen in chorea. If the patient is carried from bed to bed, the most violent reactions take place in the legs, and the attendants must exercise care not to be struck by them. These contractions take place when the patient is asked to move the limbs voluntarily. The only thing she can use moderately well is snuff tobacco. To do this she makes a sudden violent effort with the hand in which she holds the snuff, at the same time moving her head towards it; by the sudden combined movement of head and hand the snuff reaches the nostrils." He described the toes as "being strongly flexed." A further statement of interest, because it has been supposed that only more recent authors have stressed this point, is that sensibility he found in places diminished and delayed.

Interest in the differentiation of this type from various other cord diseases, notably tabes and syringomyelia, now went on apace, and in 1849, Frerichs diagnosed clinically a few cases as examples of spinal sclerosis. Although much adverse comment was made on these diagnoses, yet in 1856 one of his pupils, Valentiner, was enabled to publish their subsequent history with autopsy reports and pathological findings. These established with certainty the brilliant correctness of the diagnosis. The pathology of the cord is described by Frerichs as "an abnormal firmness of leathery consistency in irregularly circumscribed parts of the white, rarely involving the gray matter of the cord, with a poverty of blood-vessels. The patches are almost normal in color or milky white, dull and occasionally grayish red. There is a loss of nerve elements." Frerichs stated that clinically the

following characteristics of the disease had been observed: (1) The condition is produced gradually with exacerbations and remissions; (2) one side of the body is first affected, then the other; (3) paresis of the lower extremities appears early and reaches a high degree; (4) the disturbance of motility outweighs that of sensibility; (5) the chief seat of the disease is in the medulla with disturbance of the 9th, 10th and 11th cranial nerves; (6) there are frequent psychic episodes; (7) sclerosis of the nervous system is more frequent in the young; (8) the general nutrition, for a long period remains undisturbed.

In the same year, 1856, Carl Rokitansky published in his "Pathological Anatomy," a description of the connective-tissue new growth in the central nervous system, especially at the convexity of the brain through the pons and particularly in the medulla and thence through the cord. "Connective-tissue proliferations are found in the cord in the so-called slowly produced paraplegias in normal gray matter. At times the contraction produced thereby is so great that the cord seems a series of knotted strands." He then states that "at times the condition is continuous with the spinal nerves and is then known as tabes dorsalis." So unclear were the concepts of spinal cord disease even among the masters of a short time ago! In 1863, Rindfleisch went somewhat further in the pathological description in that he recognized the changes that took place in the blood-vessels and nerve elements as being produced by either a constantly recurring or else a long-standing inflammatory condition combined with hyperemia. He recognized the perivascular cell infiltrations with the thickened vessel walls and the fatty changes in the neuroglia cells. Leyden in 1863 summarized the knowledge of the day and showed that multiple sclerosis and the so-called chronic myelitis were one and the same disease. It may be interesting to give the important aetiological factors as Leyden saw them sixty years ago. First, women were attacked much more often than men,—in the proportion of twenty-five to nine; secondly, the onset occurred chiefly between the ages of twenty and twenty-five years; thirdly, only one published case was hereditary; fourthly, two great factors were exposure to dampness and

cold and concussions of the body; fifthly, psychic effects were important in the production of the disease, any sudden fright and prolonged worry; and finally, antecedent acute disease might bring on the sclerosis. As to prognosis, Leyden stated it to be unfavorable, although at times, especially in acute cases, moderate and even complete restoration might occur.

But it remained for Charcot and his school in the sixth and seventh decades of the last century, following the close study of many cases, to crystallize the earlier observations and to publish the symptomatology and pathology of the disease much as we know it today. The Charcot triad of the cerebrospinal form of the disease,—nystagmus, intention tremor, and scanning speech,—is classic. The relative immunity of the axis cylinder from the sclerotic process was also accentuated by him. At this period, furthermore, it began to be thought that the sclerotic process was an endogenous one and not secondary. Following Charcot, many observers now began to add to our knowledge of the disease, but always within the framework outlined by the great Frenchman. So Oppenheim began to lay stress upon the sensory findings, which had either been unobserved before or else much neglected, basing the anatomical situation of the larger sclerotic patches in the cord on disturbances in reciprocal sensory cutaneous areas. Strümpell describes the nature of the reflexes and lays special stress upon the disappearance of the abdominal and epigastric responses, and Uthoff in 1889 published a comprehensive monograph going into the details of the eye symptoms, more especially retrobulbar neuritis, the various types of scotomata and contractions in the visual field. Since then the advance has largely been on the clinical side in the addition of minutiae and the nicer points in diagnosis. Of late years, many cases that have conformed in part to the symptomatology of multiple sclerosis have been diagnosed as such only to have the necropsy deny the allegation. American neurologists especially, have been keen to point out clinically that so many cord conditions may simulate multiple sclerosis that many incorrect diagnoses are made and that the correct diagnosis can possibly be made only at the post-mortem examination.

As far as pathological advance since Charcot's time is concerned, the idea of multiple sclerosis being an inflammatory condition has found many supporters. The debate had at first hinged upon the question of the disease being either a primary or a secondary sclerosis. Marie believed it to be dependent upon an antecedent infectious disease, while others believed it to be due to trauma as well. Only in very recent years has the view that multiple sclerosis is a disease *per se* begun to obtain more and more supporters. Marburg frankly stated a decade ago that in his opinion the disease is a specific inflammatory one. The pathology had unfortunately been confined to the descriptive efforts of the pathologists and not to the genesis of the changes. This now seems in a fair way to be remedied.

In 1913 Bullock, now Gye, an Englishman, claimed to have transmitted the disease from man to rabbits. At present these findings have not been sufficiently corroborated. But in many centers work on the pathogenesis of multiple sclerosis is proceeding. Kuhn and Steiner (1917) with injections of cerebrospinal fluid from cases of multiple sclerosis into guinea-pigs or rabbits claim likewise to have produced typical multiple sclerosis in the operated animals. Marinesco (1919) obtained with similar methods negative results, as likewise did Siemerling and Raecke. Of interest is the finding by Kuhn and Steiner and by Marinesco of a spirochete in the spinal fluid and ventricals of their operated animals; and of more absorbing interest is the fact that Siemerling (1918) and Büscher (1920) independently found spirochetes after death in human cases that they considered disseminated sclerosis. And finally, Gye again, of the National Institute for Medical Research in Great Britain published, no later than this year, the results of his experiments in the transmission of the disease to rabbits. His own conclusion is that disseminated sclerosis is probably an infectious disease and that the virus may sometimes be found in the cerebrospinal fluid.[5] He presumably succeeded in transmitting the disease to two rabbits in ten. Control work has as yet not been published by him. This brings us to the present.

An historical perspective over the entire field from the first observations of Galen to the present meeting, resembles

microscopically the geologic ages. For almost two thousand years, during the period of cloistered learning, there was no advance whatever. Suddenly, beginning in England and France eighty years ago, the glimmering of a recognition of the existence of this special form of spinal disease began; then followed a quiescent period of fifteen years with a gradual assimilation of the facts coupled with a growing familiarity with the disease. A crystallization of the elements of the picture followed and the entity of the disease was established. We are now on the threshold of the next chapter in its genesis.

Multiple Sclerosis from the Standpoint of Geographic Distribution and Race*

Charles B. Davenport, Ph. D.

The results of the tabulation of multiple sclerosis as one of the defects found in drafted men are plotted on the accompanying map (Fig. 1). The map shows that the maximum rate found for this diagnosis was in the States of Michigan and Minnesota, each 18 per 100,000. The Michigan rate depends on 6 cases so diagnosed by local boards and 9 at Camp Dodge. Excepting Delaware and the District of Columbia (whose rates depend on one and two cases respectively), the next highest ratio is that for Wisconsin, 14 per 100,000, where 5 cases were found by local boards and 6 by examiners at Camp Grant. It is of great interest that these states of high ratio for multiple sclerosis are adjacent states, bordering on the Great Lakes. Since examinations were made at three different camps the result cannot be ascribed to the idiosyncrasy of a psychoneurological examiner at one camp.

The nearest approach to the distribution of multiple sclerosis found in any other disease is given by goiter, exophthalmic goiter, chorea, varicose veins, varicocele and allied diseases and by various heart diseases and defects. The cardiovascular diseases are associated with the tall stature of the men living about the Great Lakes—largely Scandinavians. The resemblance between the distribution

* Owing to the unavoidable absence of the author of this paper, it was presented by Dr. Pearce Bailey of New York City.

of multiple sclerosis and chorea is considerable except that chorea is abundant also in Texas, Mississippi, Missouri and the states of the North Atlantic coast and of the eastern slopes of the drainage basin of the Ohio River. That is, high rates for chorea are more widespread than for multiple sclerosis. It is rather interesting that especially high rates

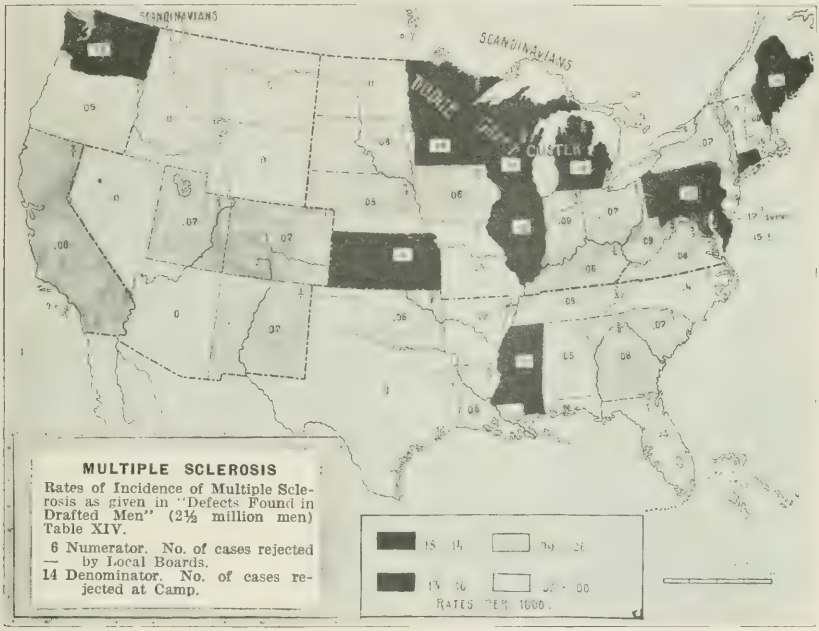
SCANDINAVIANS
SCANDINAVIANS
DODGE
CUSTER
MULTIPLE SCLEROSIS
Rates of Incidence of Multiple Sclerosis as given in "Defects Found in Drafted Men" (2½ million men) Table XIV.
6 Numerator. No. of cases rejected — by Local Boards.
14 Denominator. No. of cases rejected at Camp.
RATES PER 10000.

Fig. 1. Map of the United States showing by states the varying density rate of multiple sclerosis. "Dodge," "Grant," and "Custer" in the Great Lakes region are the names of camps at which the drafted men from those localities were mobilized. From "Defects Found in Drafted Men." (*Arch. Neurol. and Psychiat.*)

for chorea, as for multiple sclerosis, are found outside the Great Lakes region also, in the States of Washington, Mississippi and Maine.

The resemblance of the distribution of multiple sclerosis to that of simple goiter is somewhat striking. In both diseases comparatively few cases are found south of the Ohio River. The maximum rate is in Michigan, Wisconsin and the extreme Northwest.

Various hypotheses are suggested for these facts. One is that there is some race inhabiting the Great Lakes region and the State of Washington that is especially subject to multiple sclerosis as well as goiter, chorea and cardiovascular defects. One thinks of the big Swedes that live in this country. Probably the cardiovascular defects are associated with the tall stature of men from this locality. The goiter is supposed to be due to the absence of iodine in the potable waters. Whether or not chorea and multiple sclerosis are especially common among Scandinavians cannot be definitely asserted. The matter is considered further on in this paper. It is, of course, possible that in the rapid diagnosis of local boards and camps some cases of chorea may have been diagnosed as multiple sclerosis and vice versa.

Urban and Rural. For the United States as a whole, the defect rate found in the draft was, for multiple sclerosis, 0.10 per 1,000, i.e., 10 per 100,000 of the population examined. The urban rate was 12 per 100,000 and the rural rate 8 per 100,000; thus the urban rate is one-half greater than the rural rate. For four large cities (combined) the rate is 14. The rate for each city is: Philadelphia, 23; Boston, 15; New York, 13; and Chicago, 11.

Sections and Groups of Sections. The rate per 100,000 men examined in the draft was as shown in table I.

TABLE I

RATES PER 100,000 FOR MULTIPLE SCLEROSIS "DEFECTS IN DRAFTED MEN"

For southern, prevailingly *white*, agricultural communities	7
For southern, prevailingly *colored*, agricultural communities	6
For northern agricultural communities, prevailingly native *white*	8
For northern agricultural communities, prevailingly *foreign*	10
For mining sections	7
For maritime sections	10
For mountain sections	2
For the "mountain whites" of the South	7
For Indian Sections	1
For Scandinavian Section	16
For German and Austrian districts	10
For Finn Sections	29
For French-Canadian Sections	8

The high ratios found in Scandinavian and Finn Sections are probably significant. However, both "Finn Sections" are in the Great Lakes region, which is a region of high multiple sclerosis rate.

Racial Distribution. Attention was called at a meeting of the New York Neurological Society in 1902 to the low incidence in New York City of multiple sclerosis among the nervous cases. The rate stood at from 2 to 7 per 1,000, except that Dr. Onuf found among 500 to 600 cases 14 per 1,000 and Fraenkel found among Jews at Montefiore Home, 18 per 1,000.

In 1903 Taylor and Myers found only 1 per 1,000 among nearly 10,000 nervous cases in Boston. They called attention to the great difficulties of diagnosis. If certain ataxic paraplegias, diffuse degenerations and spastic paraplegias were admitted the rate would be increased to 4 per 1,000.

Van Wart in 1905, on the basis of 500 nervous cases in New Orleans, finds a rate for multiple sclerosis of 44 per 1,000 and concludes that in Louisiana and the surrounding states, multiple sclerosis is an extremely frequent disease. But this may well be due to the idiosyncrasies of the examiners. Perhaps a prevailing tradition is responsible for the high rate for this disease in Mississippi at the time of the draft.

For other countries the rate is said to be much higher than the 2 to 7 per 1,000 in New York City. Thus the Bramwells (1903, 1915) find a rate first of 20, and later of 32, in Scotland and the North of England. Williamson is said (Collins and Baehr, 1914) to have found a rate in Manchester of 27 per 1,000 and the National Hospital for Paralyzed and Epileptics in London of 60 per 1,000 "nervous cases"; but in this hospital the nervous cases were a more rigidly selected lot than in many of the other instances, so that multiple sclerosis formed a larger proportion of the population than in other hospitals.

According to Jelliffe (1904) Jolly of Berlin found 8 per 1,000 multiple sclerotics among nearly 10,000 nervous cases; and Sanger of Hamburg about 10 per 1,000.

Various authors, such as Jelliffe (1904) and Collins and Baehr (1914) give statistics concerning the racial constitu-

tion of the patients found with multiple sclerosis. But in a country whose racial composition changes so rapidly by migration it is difficult to make any satisfactory racial rates from them. Also, there is reason for thinking that there is a racial *selection* for particular clinics. Thus private patients are more apt to include an excess of native Americans and Germans and the hospital clinics of the later immigrants. The excellent provision made for Jewish patients in special hospitals for the race, diminishes the Jewish rate in the general hospitals.

However, the following statistics may be cited. My assistant, Miss Louise Nelson, has taken statements concerning the birthplace of 70 foreign-born patients with multiple sclerosis from the records of Montefiore Home, Neurological Institute, St. Luke's Hospital and Post-Graduate Medical School.

It appears that, according to the bulletin of the U. S. Census Bureau, the number of foreign-born persons per 1,000 in Greater New York was for the leading countries as given in column 2 of Table II. The proportion that each number makes of the 1,990,000 foreign-born persons has been calculated for the 7 leading nationalities. It is given in column 3. The absolute number of cases of these same nationalities found by Miss Nelson is given in column 4. The proportion that each is of the 70 foreign-born patients with multiple sclerosis is given in column 5. Were the patients distributed among the nationalities in the same ratio as the whole foreign population, columns 3 and 5 should be closely similar. Actually they show striking differences. Thus the Russians and Italians are far below expectation. The Irish are slightly above, the English and Germans have about twice as many cases of multiple sclerosis as expected; Sweden has about 2.5 times and Norway about 3.6 times. Without laying any stress on the exact multiples we have relatively more cases of Scandinavians with multiple sclerosis in the hospitals named than we would expect were cases of any nationality equally apt to go to these hospitals and were the rate of incidence the same in all nationalities. While we cannot assume the first to be true, still there is no obvious reason why it should not be approximately true.

If this be granted it would follow that there is probably an exceptionally high incidence of multiple sclerosis among the Scandinavians. Incidentally it may be said that Jelliffe's figures seem to show the same thing, i.e., more Scandinavian patients in a New York City clinic than Russians. When we recall that in the draft statistics the rate for multiple sclerosis is high in states with a large proportion of Scandinavians, it does not seem unwarranted to suggest the hypothesis that the Scandinavian race may be especially subject to this disease.

TABLE II

RATES OF VARIOUS FOREIGN NATIONALITIES IN NEW YORK; AND IN MULTIPLE SCLEROSIS POPULATION

1 Name of nation	2 No. in Greater New York (1920) in thousands	3 Proportion of total foreign-born population of 1,990,000	4 No. of cases of multiple sclerosis listed in the four hospitals	5 Proportion of entry of column 4 to 70 foreign-born cases
Russia	480	24.1	9	12.9
Italy	389	19.6	11	15.7
Germany	194	9.8	12	7.2
Ireland	203	10.2	8	11.5
England	71	3.6	5	7.2
Sweden	33	1.7	3	4.3
Norway	24	1.2	3	4.3

It is only right to add that a visit to the Swedish Hospital, Brooklyn, since the above was written, did not reveal any cases of multiple sclerosis there nor listed upon the records of the Hospital. However, this hospital does not receive many nervous cases.

The negro race is not immune from the disease; although, as indicated by Table I, it—including mulattoes—is probably less subject to the disease than the white race. Miura (1911) states that the disease is infrequent in Japan, while amyotrophic lateral sclerosis is common.

Heredity. If there is in multiple sclerosis any racial tendency in the strict sense of the word, then there is an

heredity-factor in multiple sclerosis. Usually inquiry of the patient elicits no evidence of the disease or anything like it in other members of the family. In other cases positive evidence of recurrence in the family is obtained. Whether we have to do in multiple sclerosis with two diseases, one of which follows an inflammation and degeneration of the nerve sheaths and the other of which is a primary hyperplasia of the glia is uncertain. Just as multiple neurofibromatosis is hereditary, so the latter type of multiple sclerosis might well be, but the former less definitely so.

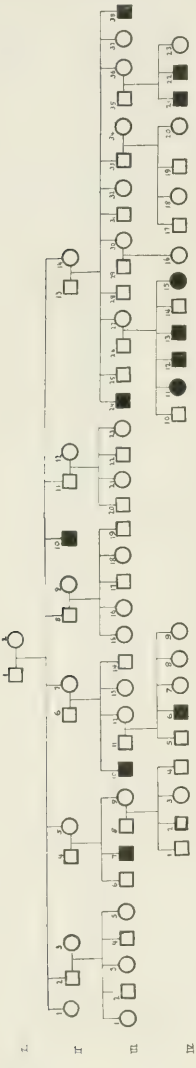

Fig. 2. Eickhold pedigree of multiple sclerosis of Tübingen and vicinity, Germany. The squares represent males and the circles females. The dark symbols indicate those affected with the disease. The earliest generation is represented by the top line. Merzbachers, *Arch. Rassen u. Gesellsch.*, Biol. vi, 1909. (*Arch. Neurol and Psychiat.*)

Since it is impossible at this time to draw any such distinctions, it will have to suffice to consider a number of pedigrees of families containing one or more cases regarded from symptoms as probably multiple sclerosis.

The most famous case is that first described by Pelizaeus (1885) and continued twenty-four years later by Merzbacher (1909). The pedigree chart (Fig. 2) as shown herewith is from Davenport's "Multiple Sclerosis from the standpoint of Geographic Distribution and Race" (*Arch. Neurol & Psychiat.*, July, 1922, viii, 51). Some authors doubt the diagnosis in this case and would classify it as an hereditary type of "cerebral diplegia."

Another considerable pedigree is contributed by Batten and Wilkinson, 1914. Here, as in Merzbacher's case, chiefly males are affected and the tendency is passed on by mothers

who are not themselves affected. This reminds one of the ordinary sex-linked type of heredity.

Numerous hereditary data for the disease have been brought together by Klausner (1901) and Röper (1913).

The recurrence of the disease in two generations is not

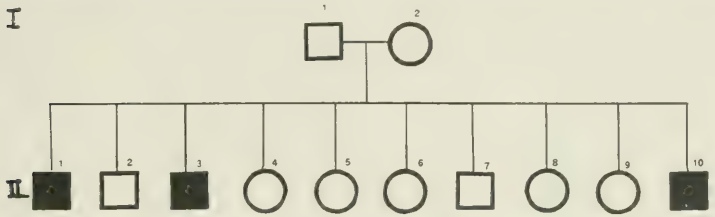

Fig. 3. Pedigree of multiple sclerosis, showing three sibs affected. Pauly et Bonne, *Rev. de méd.*, Paris, 1897. (*Arch. Neurol. and Psychiat.*)

common in typical multiple sclerosis, and where it does occur, usually the mother and child are affected. Such is first noticed the case of Eichhorst (1896). Here a woman weakness in the legs, which finally no longer would hold her, and tremor set in. The speech became disturbed and scanning. There was horizontal nystagmus—the optic

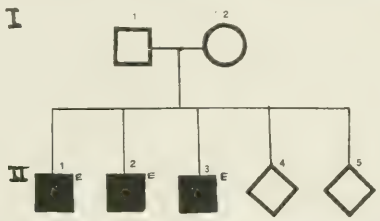

Fig. 4. Pedigree chart of parents and their children; a Bohemian family. The three dark symbols represent three sons with multiple sclerosis and epilepsy. There are also two normal children and two who died in infancy. Abrahamson, *J. Nerv. & Ment. Dis.*, 33: 200, 1906. (*Arch. Neurol. and Psychiat.*)

papillæ appeared pale. Intention tremors developed. Multiple sclerosis all along the cord was found on autopsy. Her son showed tremors shortly after his birth in 1879; he showed leg weakness in 1887; then diminished vision, nystagmus and scanning speech. Autopsy showed sclerotic changes in the cord only, as in the mother. Groups of atrophic nerve fibers

were found, especially in the anterior roots. There were three normal children.

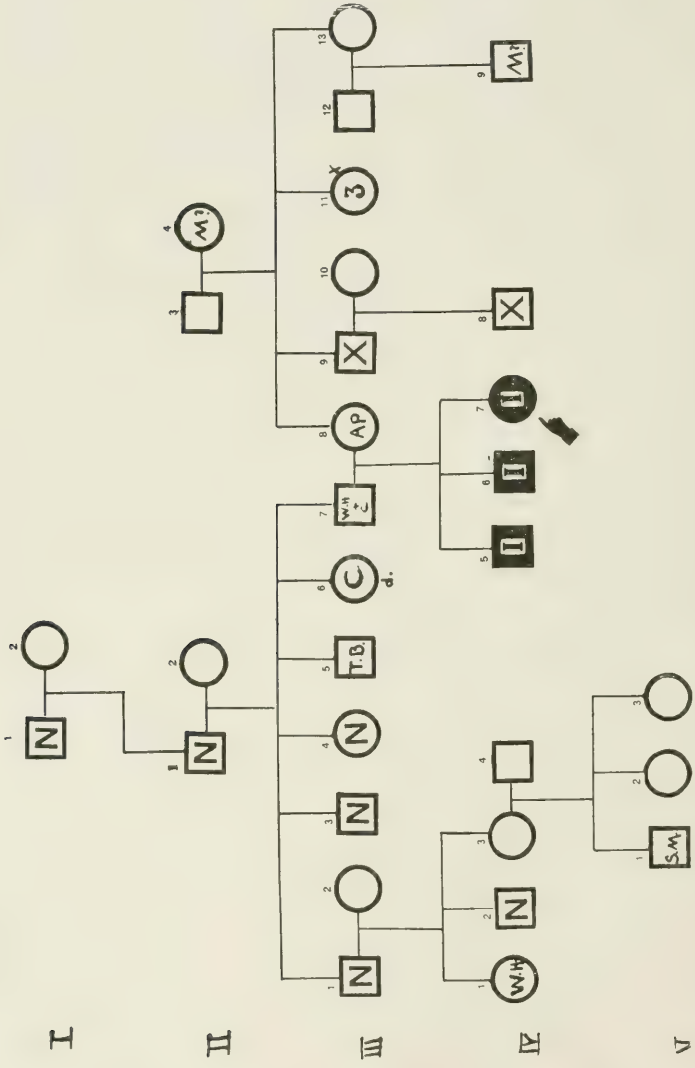

FIG. 5. Pedigree chart of multiple sclerosis in case of R. J., Central Islip State Hospital. *N* indicates normal; *M?* mentally questioned; *AP*, died of apoplexy, *T.B.*, tuberculosis; *C*, cancer; *W.H*, &c. *C.*, weak heart and cardiac disease; *S.M.*, spinal meningitis; *I*, insanity; *X*, little known; dark symbols, multiple sclerosis. (*Arch. Neurol. and Psychiat.*

Klausner (1901) gives an account of nervous "heredity" in 31 of his patients. In one the mother has been paralyzed in the arms and legs for sixteen years, and the daughter

began to have symptoms of multiple sclerosis at eighteen years of age.

In one of Röper's (1913) cases a mother had paralysis agitans and two sons had typical symptoms of multiple sclerosis.

According to Bramwell (1915) Lenot described a case of mother and child, each with multiple sclerosis. A similar history, with paralysis in the grandmother, was found in

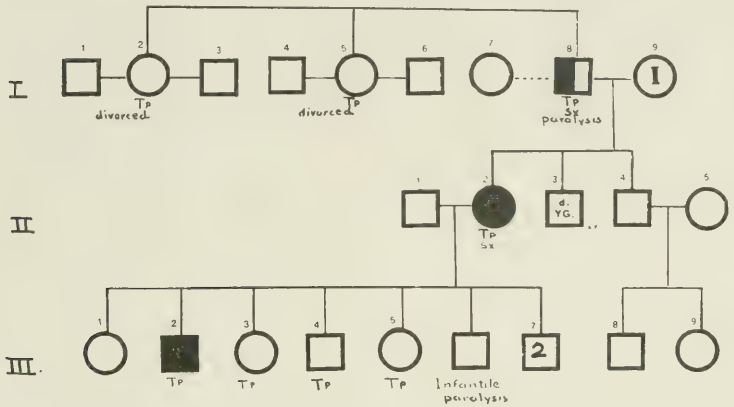

Fig. 6. Two cases of definitely diagnosed multiple sclerosis and a third doubtful (paralysis). I, 8 the grandfather, temporarily in hospital in England for trouble with hand, regarded as some form of paralysis. One of his two daughters is at the Montefiore Home with well defined multiple sclerosis. A son of this daughter died at the same Home with similar diagnosis. The other 6 living children, mostly younger, are well. Tp, liable to outbreaks of bad temper. *Sx*, erotic, sex offender. *d. yg*, died young. *I-K* fam. E. R. O. A 331: 43–51.

one of the patients at Montefiore Home, November, 1921 (Fig. 6).

Cestan and Guillain (1900) describe the case of a boy of fifteen years with a paraplegia, highly exaggerated knee—and ankle—jerks, positive Babinski, but no speech or macular defect or intention tremors. His father and eldest sister presented the same symptoms.

Cases of uncle and nephew with the disease have been described by Reynolds (1904) and Curschman (1920), (Fig. 7).

In many cases some nervous defect, such as weakness in gait, tremors, paralysis agitans, progressive paralysis, has been described in one of the parents of the patient.

But far and away the commonest condition of recurrence of the disease in the family is that of two or more affected persons in the same fraternity. (Fig 3 & 4.)

In conclusion, may I be permitted the suggestion that, whatever may be eventually proven to be the endogenous cause of multiple sclerosis, the factor of heredity cannot be

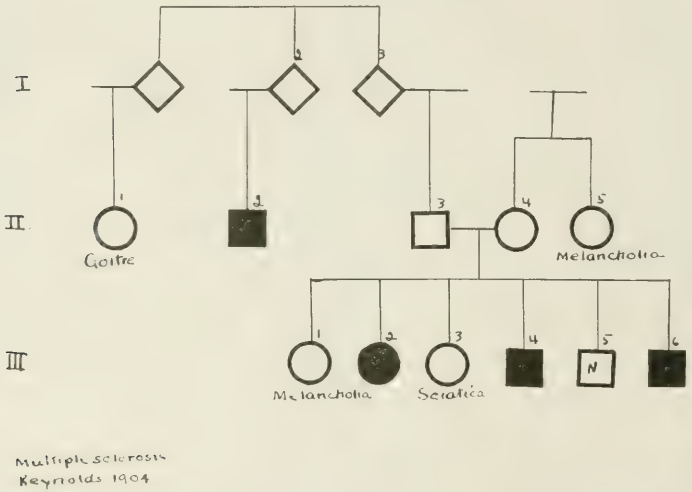

FIG. 7. Three out of 6 siblings have multiple sclerosis. A cousin of the father is similarly affected. Reynolds, 1904. *Brain*, XXVII, 161–9.

left out of account? Just as tumors inoculated into a mouse will, or will not, grow, according to the racial constitution of the mouse; and just as the bacillus tuberculosis that inhabits the body of all of us does or does not flourish there depending upon the constitution and condition of the individual; so there are probably internal conditions that inhibit, and others that facilitate the development of this disease or the endogenous factors upon which it depends. And so it comes about that the manifestations or symptoms of the disease differ in different persons; and that they are sometimes very similar in closely related individuals, because the hereditary factors of the constitution in which they operate are similar.

It seems most probable that such geographical, ethnological and familial distribution as multiple sclerosis shows depends in part upon one or more hereditary factors.

Incidence of Multiple Sclerosis in United States Troops

Pearce Bailey, M. D.

During the recent mobilization the neuropsychiatric officers examined approximately 3,500,000 men, draftees and volunteers. The examinations were made at the camps, and in the case of draftees, after acceptance by draft boards.

A total of 69,394 cases of nervous and mental disease and defects were identified. They were divided into nine clinical groups. The subhead under which multiple sclerosis was classified was entitled "Organic Diseases and Injuries." It included injuries, the general organic diseases of the nervous system, syphilis of the central nervous system (exclusive of paresis), a few minor conditions, such as tics, myasthenias, myotonias and other conditions. This group embraced 6,916 cases, about one-tenth of the total number.

Our method of approach to a determination of the frequency of multiple sclerosis is to determine its frequency, not in relation to the number of men examined, but in relation to other nervous conditions found in the particular group to which it belongs. For example, among 6,916 so-called organic cases, there were 511 cases of multiple sclerosis. We may say, therefore, that multiple sclerosis has a distribution average among organic conditions of 7.4 per cent.

Variations from this average occurred in certain states and in certain races. The variations in states was in approximate agreement with the results given in "Defects Found in Drafted Men." The variations as to races are given in Table III.

Of the fractions given in the table, the numerator indicates the number of cases of multiple sclerosis found in the race, and the denominator indicates the total number of cases of general organic conditions in that race. The resulting percentage is the percentage of cases of multiple sclerosis as compared to organic conditions in that race. It will be ob-

served that the percentage of cases of the disease in the Scandinavians, the French, the Slavs, the Scotch, the Germans, the English and the Irish all exceed the general distribution rate of multiple sclerosis. Also, there was an excess of cases in the foreign-born as compared with the native-born.

The average of foreign-born in the whole group of organic conditions was 9.2 per cent, while in multiple sclerosis it was higher, namely, 12.7 per cent. Thirty per cent of the patients with multiple sclerosis gave a family history of nervous diseases (as compared with syphilis of the central nervous system, for example, in which only 7 per cent of the patients had a family history of nervous diseases); 10 per cent gave a family history of mental disease.

TABLE III

PERCENTAGE DISTRIBUTION OF MULTIPLE SCLEROSIS AMONG INJURIES AND DISEASES OF THE NERVOUS SYSTEM AS DETERMINED IN CERTAIN CLASSIFIED RACES

Total number of cases of nervous diseases and injuries.... 6,919
Total number of cases of multiple sclerosis..... 511

Average distribution rate of multiple sclerosis, per cent.. 7.4

	Cases of multiple sclerosis	Cases of general organic disease	Percentage
African	28	800	3.5
Dutch	4	38	1.0
English	74	913	8.1
French	11	102	10.7
German	35	418	8.3
Irish	41	516	7.9
Italian	10	191	5.2
Scotch	8	96	8.2
Scandinavian	16	127	12.5
Slav	18	181	9.0

The following questions submitted to Dr. Bailey before the Commission, together with the answers to them, are here reported verbatim.

Dr. Taylor: Is it not probable that the number would be larger than you have estimated, if more careful examinations had been possible? I presume the examinations in these cases and the determinations were made on more or less particular cases. Do you think many cases, in other words, escaped the observation of the examiners?

Dr. Bailey: I do not think very many of them did, for the reason that our examination extended over an average of six months, being the average period between arrival at camp and being shipped overseas, and during all that period these men were available to be examined by a specialist in all the camps, and consequently I think you would have to imagine a case that slipped through as one that had no physical disability whatsoever, no symptoms to complain of.

Dr. Starr: I think it has been observed by everyone in this country that multiple sclerosis was relatively rare, as compared to what we saw in hospitals in England, France, Germany and Austria. All our textbooks have called attention to the rarity of multiple sclerosis in the United States. It has been thought by one or two observers, that the increase in the number of multiple sclerosis cases which we see at present, may be due to the fact of our increasing foreign population, and that the fact that now we see more cases than we did ten or twenty years ago, is attributable to the foreign population in the cities here, particularly in New York, where the foreign population is increasing more rapidly.

I cannot gather from Dr. Bailey's statement, from these percentages, whether there is any possible way of estimating the American percentage as related to the others. Dr. Bailey shows that 12 per cent are Scandinavians, 10 per cent French, 9 per cent Slavs, 9 per cent Germans, 8 per cent Scotch, 8 per cent English, and so forth, but I see no record, excepting "Africans," of American statistics. I have been very much impressed, with others, with the great rarity of multiple sclerosis in this country, both in public and in private practice. Some years ago, when I read a paper before the New York Neurological Society, I called attention to that fact; and I cannot believe that it has been due to oversight on my part in not diagnosing multiple sclerosis, because every time I came back from Europe, for the last twenty years, I have been looking for it, for the reason that over there I have seen so much of it and so little of it here.

Dr. Bailey: It is difficult to define this method of distribution of these cases. Dr. Starr, however, gets the wrong idea in thinking that 12 per cent of the patients are Scandinavians, another percentage are Slavs, and so on. That is not the case. Twelve per

cent of the disease among Scandinavians is multiple sclerosis, and 9 or 10 per cent of the organic disease among the French is multiple sclerosis, whereas in the general population of the army, which we may take as representative of the American population, we put down 7.5 per cent distribution, that is, of the general mass of organic diseases among the recruits; 7.5 per cent of the figure was multiple sclerosis. You can see that the Slavs and the Scandinavians exceed that by their distribution averages.

Dr. Patrick: Is this shaded map based on examinations in given camps or upon the states from which the recruits came? I noticed on the map that the names of the camps were given in the black area. Does that mean that these statistics were based on a series of examinations made in the camps, or were the states from which the recruits came the basis of the distribution?

Dr. Bailey: I think that is purely by states. Even if done at camps, it referred back to the states from which the recruits came. I make that statement because that was the method used in compiling "Defects Found in Drafted Men."

Dr. Strauss: I would like to ask, when we come to make statistical studies, whether it is not our feeling that a great deal as to heredity, cannot be drawn from such studies because of our lack of knowledge of the cases upon which the statistics are based? As you look over charts, such as are presented here, you see that an antecedent of the third generation before is designated as having an awkward gait. Now, as physicians, does that mean anything to us, when we come to judge of it as a hereditative factor, because he might have had flat-feet or bow-legs, or some other condition?

Furthermore, you see an antecedent is designated as "nervous." Again, it seems to me that that is a term applied to an individual, upon which we cannot lay much weight, especially if one is not in contact with the antecedent or the antecedent is not examined by a person familiar with what "nervous" means, but one has to depend upon field work in getting this information from some member of the family, who, for all we know, may have gotten that knowledge by hearsay. In other words, is there not in this part of the work quite an element of error?

Exogenous Causes of Multiple Sclerosis

Lewellys F. Barker, M. D.

The possible exogenous causes that I have to consider are: (1) The influence of earlier infections; (2) the influence of intoxications; (3) thermal and electrical influences, and (4) traumata.

With the aid of Dr. Caroline Latimer and Miss C. J. Smith, I have analyzed 44 cases, part of them from my private practice, part of them from the records of Johns Hopkins Hospital, all of them studied between 1905 and 1921.

Infections. It was suggested by Pierre Marie of Paris, and the suggestion has been favorably entertained by various neurologists since, that multiple sclerosis might be a sequel of various infectious diseases. Typhoid fever, malaria, influenza, acute rheumatic fever, diphtheria and the childhood infections (like measles, scarlet fever, etc.) have been especially mentioned. It has been observed in a certain number of cases, not in many, however, that the symptoms of multiple sclerosis began to appear soon after the occurrence of an infectious disease in the same person. It is possible that in some of these cases it was a disseminated encephalomyelitis rather than a true multiple sclerosis that was dealt with. It must be remembered that this relationship may have been purely accidental. Unless the infection and the onset of the multiple sclerosis are closely related in time to one another, there could be but little justification in considering the multiple sclerosis as a sequel of the infection. It has been fairly well established that a multiple sclerosis already in existence may undergo exacerbation from intercurrent infection. Its so-called "beginning" may have been called forth by the infection.

If we take into account only cases in which an infection has preceded the apparent onset of multiple sclerosis by, say, two or three months, not longer, the statistics in the literature indicate that only from 3 per cent to 5 per cent of all the cases of multiple sclerosis recorded show such a temporal connection with infection (Berger; Hoffman). In this country Woodberry (1919) has emphasized the coexistence of chronic tonsillar infections; Gill and Bassoe call attention to the frequency of both tonsillar and dental infections.

In the cases that have occurred in my own consultation practice and in the Johns Hopkins Hospital, there was a history of one or another infection shortly before the onset of the symptoms of multiple sclerosis in 5 of the 44 cases; these infections included gonorrhea (1), tonsillitis (1),

nasopharyngitis and otitis (1), abscessed teeth (1), and influenza (1).

In the distant past of the cases analyzed, childhood infections were as common but no commoner than in other patients.

Since the outbreak of epidemic encephalitis in 1917, there has been noted the occurrence of a certain number of cases in which the disease became chronic, with exacerbations, but in the few autopsies that have been made upon such cases, the lesions found have not been those of multiple sclerosis.

Intoxications. It was thought by Oppenheim that poisoning by mineral substances, especially metallic substances like lead, arsenic and tin, might be responsible for the origin of multiple sclerosis, and von Jaksch believed that poisoning by manganese could give rise to a clinical picture resembling multiple sclerosis if not identical with it, but when we consider the total number of cases of multiple sclerosis met with, a history of poisoning by metals is rare among them. Multiple sclerosis is probably just as common in women as in men, or nearly so, and women are not exposed to metal poisoning. Again, in the majority of cases the disease begins in early life often at a period before the patients could have been subjected to metal poisoning from their occupations. Further, it is scarcely conceivable that the successive exacerbations that are characteristic of the disease can be explained on the ground of a succession of metal poisonings. In my series of 44 cases, a history of metal poisoning is found in none.

Other poisons that have been incriminated include alcohol and carbon monoxide. Jelliffe mentions alcoholism in 8 per cent of his cases, a larger incidence, however, than is found in most statistics. Among my 44 cases there were only 2 patients who used alcohol to excess; the majority were total abstainers. When one recalls the enormous number of cases of alcoholism formerly seen and how rare it was to see multiple sclerosis in an alcoholic addict, it would seem improbable to think that it could be other than a predisposing factor or exacerbating factor. The same comment may be made upon the relation of carbon monoxide poisoning to multiple sclerosis. Disseminated lesions throughout the brain and spinal cord may, it is true, occur in carbon-monoxide poison-

ing, but these lesions do not appear to be identical with the lesions of multiple sclerosis.

Thermal and Electrical Influences. In some of the cases of multiple sclerosis one finds a history of heat stroke, of lightning stroke, or of exposure to cold and wet. But such instances are rare and the hypotheses that have been put forward to explain them (reflex contraction of vessels in the central nervous system due to cold; chemical changes in hemoglobin brought about by thermal influences) seem forced. Krafft-Ebing reported thermic injury in no less than 40 of 100 cases. However, critical observers express the opinion, that these thermal influences are not the causes of multiple sclerosis, but, at most, are injuries that cause an exacerbation of an already existing disease.

In our Baltimore series of 44 cases, the analysis does not reveal a single instance in which there had been electrical injuries, thermal injuries, or marked exposure to cold or wet.

Traumatism. Patients who suffer from chronic nervous diseases are prone to incriminate traumata, either physical or psychic, as causative agents. Neurologists, who see many patients suffering from epilepsy, brain tumor, mental deterioration, and other organic processes, are very familiar with the prevalence of this conception. Similarly, multiple sclerosis is not infrequently attributed by patients, by their friends, and sometimes by physicians, to traumatic causes. It has been assumed that the trauma injures the blood-vessels, does harm by violent commotion in the cerebrospinal fluid, or by concussion causing molecular changes in the nerve substance, or by tearing lymph spaces with resulting necrosis in the parenchyma. No one has, however, been able to reproduce the lesions of multiple sclerosis through experimental traumatism to animals.

If, before assuming that multiple sclerosis is due to trauma, one adheres to the requirements laid down by K. Mendel, the incidence is small. Mendel laid down as necessary conditions: (1) Direct injury to the skull or spine or violent shaking of the same; (2) exclusion of every other cause; (3) demonstration of complete health before the trauma, and (4) demonstration of a definite temporal connection between the appearance of the first symptoms of the

disease and the accident. The incidence, when these conditions are more or less regarded, varies according to different authors: 8 per cent (Schultze), 9 per cent (Berger; O. Marburg), 12 per cent (Jelliffe).

It must be remembered that injuries often occur in multiple sclerosis as a result of, rather than as a cause of, the disease, and when the multiple sclerosis appears to develop after trauma a very careful inquiry into the previous history will often reveal the fact that symptoms of the disease had been present earlier.

It does seem certain, however, that a latent multiple sclerosis may suddenly become manifest after a severe trauma (either physical or psychical) and that a multiple sclerosis that has already been manifest may undergo marked exacerbation after trauma. The question comes up not infrequently in connection with suits for damages.

In the Baltimore series of 44 cases, 11 patients gave a history of physical trauma of one or another sort, and 3 gave a history of nervous and mental strain. However, in most of the instances, the trauma occurred long before the onset of the illness; in only 3 cases did it occur within a year of onset, at any rate as far as the patients' knowledge was concerned. Three of the female patients stated that the onset and progress of the disease seemed to be related to child-bearing.

Conclusions. If multiple sclerosis is a disease entity due to a single cause that acts in early life, it may be due to some specific infection, but the evidence available is strongly against its being caused by any of our well-known infections, by any ordinary intoxication (organic or inorganic), or by electrical, thermal or traumatic influences. If the exogenous factors mentioned play any rôle at all in the etiology of the disease, they must act either as predisposing influences for the true cause, or as aggravators of a disease already started by the true cause.

Statistics of Multiple Sclerosis

Israel S. Wechsler, M. D.

Introduction. This study is based on the records of 1,970 cases of multiple sclerosis. Of the total, 1,773 represent cases culled from literature and 197 those whose records

I have personally studied. Of the latter, 55 are from the Vanderbilt Clinic, 93 from Mt. Sinai Hospital, and 49 from the Montefiore Hospital.

The object of the investigation was to determine the comparative incidence of the disease in the United States and Europe, the ages (including the ages of onset), average duration, sex, civil status, occupation and nativity. Special study was made of cases reported as hereditary, congenital, familial and infantile. Although the matter of personality (psychic and mental manifestations) does not come within the purview of a statistical study, attention was paid to this aspect of the symptomatology of the disease.

With the exception of a few recent reports in the literature, most of the statistical records date back many years; it is particularly true of those which have appeared in this country. This fact is not without importance for the reason that the diagnosis of multiple sclerosis was more rigidly dependent on the Charcot triad in the earlier days than it is at present; many reports date back to the time when the Babinski phenomenon was unknown and when the significance of absent abdominals in multiple sclerosis was not quite appreciated. The more elastic conception of the disease on the part of European (more especially German) neurologists may account for some of the differences in the comparative incidence of the disease. It may be said, too, that the bare records do not always give correct information as to the disease, and a critical study of case reports frequently leads one to doubt the diagnosis. This is especially true of cases recorded as infantile, congenital, hereditary and familial. I have therefore taken special pains to study, as far as was possible, the histories of many of the cases of multiple sclerosis recorded in the literature, which bore on statistics, especially those of the last mentioned group. Needless to say I reviewed each of the 197 records of the cases which make up my own study. Another point of importance is the fact that, with very few exceptions, practically all the diagnoses of multiple sclerosis are made on clinical and not pathological grounds.

Discrepancies will be found in the various totals for the reason that the statistics recorded in the literature are not

uniform. Some investigators merely refer to the percentage incidence, others speak only of sex, still others only of ages or duration. American records are especially meager and, with the exception of Jelliffe's, rather incomplete. This makes comparison between American and European statistics somewhat uneven; nevertheless, there is a sufficient number of records for a fairly satisfactory comparison. Perhaps it should be pointed out that the continental statistics cover practically the whole of Europe whereas the American statistics, if not limited to New York City, embrace only a small part of the country. Some of the totals recorded by European observers in a few instances (especially in the infantile group) embrace a number of cases which have been included by other compilers in their study of statistics. By referring to the originals and by cross references I have tried to avoid recording the cases more than once.

Total Number of Cases. Of the 1,970 cases recorded 518 are from America and 1,452 from Europe. Deducting the 197 cases personally studied, there remain 321 American cases whose records date back many years, none being more recent than 1903. Most of the European statistics are not any more recent, but they are spread over a greater number of years.

TABLE I

NO. OF CASES IN THE UNITED STATES

Jelliffe	109	Fraenkel	18
Hammond	47	Sachs	15
Collins	46	Taylor	9
Stieglitz	34	Fisher	8
Starr	27	Onuf	8

Total	321
Vanderbilt Clinic (1918–20 and half of 1921)	55
Mt. Sinai Hospital (1912–1920)	93
Montefiore Hospital (1914–1921)	49
	518

NO. OF CASES IN EUROPE

Berger	207	Lent	51
Klausner	126	Lotsch	45
Bramwell	100	Mauschner	40
Kraft-Ebbing	100	Berlin	39
Hoffman	100	Birley and Dudgeon	35
Uhtoff	100	Morawitz	33
Gaehlinger	86	Blumreich and Jacob	29
Muller	75	Nolda	26
Bruns	70	Redlich	23
Jolly	59	Marburg	22
Schupfer	59	Sanger	17
			1,452
Total No. of Cases of Multiple sclerosis			1,970

Incidence. Morawitz states that it is the most common organic nervous disease in rural populations and gives the following figures: Multiple sclerosis 33 cases, tabes 20, and cerebrospinal lues 10. Cassirer says that next to tabes and syphilis of the nervous system multiple sclerosis is the most common disease. Muller also speaks of it as the most common organic disease. Neither gives figures. These statements are not quite borne out by my records. While there were 49 cases of multiple sclerosis in the Montefiore Hospital between 1914 and 1921, there were 167 cases of syphilis of the nervous system divided as follows: Tabes 85, general paresis 17, and cerebrospinal lues 65. In Mt. Sinai Hospital there were 562 cases of syphilis of the nervous system to 93 of multiple sclerosis, almost 6 to 1, divided as follows: Tabes 160, general paresis 85, and cerebrospinal lues 317. It should be explained that the Mt. Sinai figures are not statistically conclusive for the reason that during the period covered, special study of syphilis of the nervous system was carried on and effort was made to admit an unusual number of cases.

The highest percentage recorded in Europe is that by Mauschner in the Tubingen Clinic, that is 2.5 per cent. The lowest is given by Jolly (Berlin) as 0.84 per cent. Williams of England gives a percentage of 2.2. The highest of the older American statistics is that by Fraenkel, 1.7 per cent and the lowest by Taylor 0.09 per cent, even if we include

his doubtful cases.* The reason why Fraenkel's figures were high is that they represented the incidence among organic cases only. The recent Montefiore Hospital records (1914–21)

TABLE IIA

PERCENTAGE INCIDENCE IN THE UNITED STATES

Old Records

		Per cent
Jelliffe	109 cases out of 31,502	0.34
Hammond	47 cases out of 10,000	0.47
Collins	46 cases out of 9,508	0.5
Starr	27 cases out of 10,056	0.27
Fraenkel	18 cases out of 1,050	1.7
Taylor	9 cases out of 9,783	0.09
Fisher	8 cases out of 2,451	0.32
Onuf	8 cases out of 500	1.6
Total	272 cases out of 74,850	0.36

Recent Records

		Per cent
Mt. Sinai Hospital	69 cases out of 2,359	2.9
Montefiore Hospital	49 cases out of 1,144	4.3
Vanderbilt Clinic	55 cases out of 11,859	0.46
Total	173 cases out of 15,362	1.1

TABLE IIB

Percentage Incidence in Europe

		Per cent
Bruns (Hanover)	70 cases out of 5,500	1.33
Bramwell (England)	100 cases out of 5,825	1.7
Jolly (Berlin)	59 cases out of 6,979	0.84
Mauschner (Tübingen)	40 cases out of 1,602	2.5
Saenger (Hamburg)	17 cases out of 1,684	1.0
Total	286 cases out of 21,590	1.33

show a percentage incidence of 4.3 while the recent Mt. Sinai Hospital records (1912-20) give 2.9 per cent. Both these figures, representing ward (organic) cases, are lower

* Unless otherwise mentioned the percentages stated refer to the total number of cases both organic and functional.

than Bramwell's, which are 5.5 per cent for all ward cases (also presumably only organic). Bramwell's figures for all clinic patients are 1.7 per cent.

Computing all the European records together we get an average incidence of 1.33 per cent, while all the old American records gave only 0.36 per cent. These figures may be compared with what Bramwell found in 1903, that is 1:82 or 1.2 per cent in Europe and 1:219 or 0.46 per cent in the United States. The recent American figures show a percentage of 1.1 of all cases, which is three times the old ones, and almost approaches the European. Combining the Mt. Sinai and Montefiore records,* 2.9 per cent and 4.3 per cent respectively, we get a percentage of 3.36 for organic cases. It will be seen therefore, that the average incidence of multiple sclerosis in this country has risen considerably in the past twenty years; but whether due to more accurate diagnosis or extension of the disease concept or to actual numerical increase cannot be stated from the figures alone

Age. Multiple sclerosis occurs in all ages, from early childhood to very old age. It has been described in about 100 cases in children. In the literature mention is made of patients as young as one and a half and three and four years. The youngest recorded by myself was ten years, with the onset of the illness at seven. Crocq (quoted by Jelliffe) speaks of a patient of eighty-one years, but in all other records no mention is made of patients above sixty-five. The disease is most common between the ages of twenty and forty, about 70 to 75 per cent of all cases. Jelliffe records an unusually large number between fifty and sixty—18 per cent. The following tables may serve as comparisons.

* It will be noticed that the Mount Sinai Hospital percentage is computed on a total of 69 cases out of 2,359, whereas the total number of histories of multiple sclerosis numbered 93. This is because the diagnosis was doubtful in 24 cases, and I included only those in which it was absolutely certain clinically. The same applies to the Montefiore Hospital records; only of this group I excluded, besides doubtful cases, also records of patients who had previously been at Mount Sinai Hospital. Had I included the latter, and for the purpose of computing the statistics of the Montefiore Hospital alone, there is reason for doing so, the percentage incidence in that institution would have been considerably higher.

TABLE III

AGES

Combined Vanderbilt Clinic, Montefiore and Mt. Sinai Hospitals

Wechsler			*Klausner*		*Marburg*		*Muller*	
Age	No.	Per cent	Age	No.	Age	No.	Age	No.
Below 10	1	0.5	0– 5	2	10–20	4	15–20	12
11–20	11	5.7	6–10	2	21–30	9	21–30	33
21–30	65	33.5	11–20	17	31–40	6	31–40	23
31–40	72	37.0	21–30	38	41–50	1	41–50	6
41–50	36	18.5	31–40	36	51–60	1	51–60	1
51–60	8	4.1	41–50	17		21		75
61–65	1	0.5	51–60	7				
	104		61–65	2				
				121				

Berger		*Jelliffe*		*Morawitz*		*Borst* (from literature)	
Age	No.	Age	No.	Age	No.	Age	No.
0– 8	8	0 10	9	0–10	1	1– 5	5
10–20	49	10–20	8	10–20	16	6–10	10
20–30	83	20–30	21	20–30	14	11–20	45
30–40	51	30–40	27	30–40	10	21–40	306 = 70%
40–50	10	40–50	20	40–50	2	41–50	41
50–60	5	50–60	19		43	51–60	29
	206		104			51–65	2
							438

Duration. Two different conceptions are implied under the term duration. One refers to the length of the period from

the onset of the first symptom to the time the patient comes under observation, the other is the total duration from the onset of the illness to the patient's death. The first, assuming it is always possible to tell the time of onset of the first symptom, is somewhat easier to estimate than the second, for the reason that most patients are not followed up to the very end. Indeed nearly all the records refer to the first idea of duration. It is important to bear in mind these two different views in the bearing they have on prognosis, because it is perfectly obvious that the same patient whose duration under the first concept is estimated, say, at six months, may still be alive twenty years hence, and in a subsequent study be classed under the second idea of duration.

Birley and Dudgeon give the average duration from the onset of the illness to time of examination as four years, the shortest being three weeks and the longest fourteen years. Marburg gives the duration in 22 cases he studied as twenty-six days to thirteen months, one exception being three years' duration. Bramwell gives the average duration in 35 fatal cases as seven years and nine months (seven months to twenty-one years). He records the longest duration in a living patient as thirty-three years, and 6 cases between twenty and thirty years. My own records show 1 patient with a history of twenty-five years' duration. Five of my patients gave a history of one month or less. Below are comparative tables.

TABLE IV

DURATION

Combined Vanderbilt Clinic, Montefiore and Mt. Sinai Hospitals		*Bramwell*		
Less than 6 mos.	31	Fatal cases:		
7 mos. to 1 yr.	15	1– 4 yrs.	10	
13 mos. to 2 yrs.	4	5– 9 yrs.	13	
2– 3 yrs.	27	10–14 yrs.	8	
3– 4 yrs.	11	15–21 yrs.	4	35
4– 5 yrs.	15			
5– 6 yrs.	7	Alive—worse		33
7–10 yrs.	28	unimproved		16
11–15 yrs.	9	improved		8
16–20 yrs.	1	well		4
21–25 yrs.	1	Unknown		14
	192			110

Sex. The male sex is more often affected than the female, in the ratio of nearly 3 to 2. Of 26 records only 6 speak of greater incidence among females, the latter being those of Charcot, Berlin, Muller, Bruns and Stelting, Morawitz, and Birley and Dudgeon. These figures represent about 15 per cent of the total number of cases reviewed. The American and European statistics very nearly coincide in this respect.

TABLE V

SEX

Europe	*M*	*F*	*U. S.*	*M*	*F*
Berger	140	66	Jelliffe	68	41
Klausner	78	44	Stieglitz	17	17
Krafft-Ebing	58	42	Sachs	10	5
Uhtoff	67	33	Moran	4	4
Muller	35	40	Montefiore Hospital	26	23
Hoffman	53	47	Vanderbilt Clinic	36	19
Probst	34	24	Mt. Sinai Hospital	55	38
Bruns and Stelting	13	25			
Lent	37	14		216	147
Lotsch	30	15		or	or
Berlin	13	26		57%	43%
Morawitz	15	18			
Charcot	9	25			
Birley and Dudgeon	12	23			
Blumreich and Jacob	23	6			
Nolda	16	10			
Redlich	12	11			
Marburg	11	11			
Cassirer	2	4			
	658	484	Total No. of cases	874	631
	or	or		or	or
	58%	42%		58%	42%

Occupation. Morawitz states that multiple sclerosis is most common in the rural (agricultural?) population. It is said to affect mainly the laboring class. My own statistics do not at all confirm either view, though it is hardly fair to contradict the first statement, seeing that all of my cases come from New York City. Practically every occupation is represented in my list of cases, as the following table shows. Obviously all general ward patients come from the working population.

TABLE VI

OCCUPATION

Soldier	Pressman	Candy maker	Newsdealer
Cashier	Salesman	Student	Domestic
Teacher	Carpenter	Storekeeper	Bellboy
Machinist	Houseworker	Weaver	Artist
Tailor	Roofer	Printer	Chauffeur
Peddler	Cook	Baker	Iron worker
Laborer	Clerk	Cigar maker	Policeman
Painter	Driver	Bartender	
Cutter	Butcher		

Nativity. The following figures are practically limited to New York City, and it is obviously not altogether true to speak of them as representative of the whole United States. There are more than four times as many cases among those of foreign birth than among natives. Even allowing for the great number of foreign born in New York—and they constitute roughly only two-fifths of the population—it is difficult to account for the unusual excess of foreigners over natives. The fact in itself, however, may possibly account for the greater incidence of multiple sclerosis in Europe as compared to America, although in his study covering fifteen years (1888–1903) Jelliffe gives more nearly even figures: 47 native and 54 foreign born. The following table refers to my own cases.

TABLE VII

NATIVITY

	Native	*Foreign-born*
	per cent	*per cent*
Mt. Sinai Hospital	11 = 11.8	82 = 88.2
Montefiore Hospital	6 = 12.2	43 = 87.8
Vanderbilt Clinic	19 = 34.5	36 = 65.5
Total	36 = 18.3	161 = 81.7

Civil Status. Multiple sclerosis is more common among married people than among single ones, but this fact is accounted for by the greater incidence of the disease during the ages between twenty and fifty. The fact, therefore, cannot be said to have special significance. Except my own, there are no statistics bearing on this point.

TABLE VIII

CIVIL STATUS

	Married *per cent*	*Single* *per cent*
Mt. Sinai Hospital	60 = 64.5	33 = 35.5
Montefiore Hospital	23 = 60.5	15 = 39.5
Vanderbilt Clinic	35 = 63.6	20 = 36.4
Total	118 = 63.5	68 = 36.5

Multiple Sclerosis in Children. Opinions vary as to the existence of multiple sclerosis in children. In alluding to 4 cases of early multiple sclerosis which he had seen (four, seven, twelve and thirteen years respectively) Oppenheim expressed the opinion, in 1887, that "the beginning of multiple sclerosis in adults can not infrequently be traced to the very earliest childhood." Muller states that "proof of the existence of infantile multiple sclerosis is still missing, but it may trace its beginning to childhood" and "the development of the process on the basis of a congenital predisposition (is) most likely." It may be pointed out that congenital predisposition is a very vague expression, capable of numerous interpretations.

One of the early, very exhaustive studies of infantile multiple sclerosis was made by Schupfer. He studied 58 cases recorded in the literature up to 1902 and included 1 case of his own. This was a child of eleven, who at nine had an acute illness with fever, coma, convulsions, paralysis and ocular palsies. Although Schupfer includes this case in his group of multiple sclerosis it is obvious from the history, no matter what the clinical findings were at the time of the examination, that he was dealing with a case whose inception corresponds to a meningitis or meningoencephalitis. Most of the cases he records are neither clinically nor pathologically multiple sclerosis. Congenital lues would account for many of them. Hereditary spinal spastic paralysis, Friedreich's disease, hereditary cerebellar ataxia, encephalitis, tumors of the brain, cerebral palsies of children, the Little and Foerster types, all these are represented in the group recorded by Schupfer. Nevertheless, it must not be inferred that this author has not critically analyzed his material;

he would still include 28 of the 59 cases as true instances of multiple sclerosis in children.

In 1909, Gaehlinger reviewed the histories of 86 cases of multiple sclerosis out of a total of 91 reported as having occurred in children below fifteen, some even in infancy. All the cases were taken from the literature and included those recorded by Schupfer (1902) and Baboneix (1904). Gaehlinger concluded that "none of the observations has given us absolute proof of the existence of infantile multiple sclerosis." This despite Oppenheim's ingenious theory that all multiple sclerosis begins in infancy and only manifests itself later in life. Gaehlinger also emphasizes the difficulty of diagnosis. To which may be added the unreliability of most histories, the unusual difficulty in tracing the onset of the earliest symptoms and the inability to exclude fever or infectious diseases as etiological factors. The same author also mentions Friedreich's ataxia, chorea, Little's disease, cerebral sclerosis, family spastic paraplegia, tumors of the brain, disseminated lues (congenital), hysteria and encephalomyelitis, as more likely diagnoses. The recent epidemic of encephalitis justifies the addition of this disease as a likely possibility.

Eichhorst reviewed the literature up to 1896. He mentioned the 14 cases recorded by Marie up to 1883, the 19 by Unger up to 1887 and those by Nolda up to 1891. Eichhorst added a case of his own, that of a boy of eight. (His mother had multiple sclerosis, as was shown by autopsy.) The boy also died and came to autopsy. Microscopic section of the boy's cord showed multiple sclerosis. Of the other 26 cases only 3 came to autopsy. In those 3 instances the cord was not examined and the reports show that other brain changes besides sclerosis were found. Nolda's case was that of a boy of nine whose disease began at seven and whose clinical picture was typical of multiple sclerosis. Weisenburg reported the cases of a girl of four and a boy of fifteen—brother and sister.

Armand-Delille described a case of multiple sclerosis in a child of five. Raymond and Beaudouin reported the case of a girl of thirteen whose symptoms began at ten. Neither case is conclusive. Raymond and Lejonne speak of a girl of

nine whose condition was progressive and whose signs and symptoms were apparently those of multiple sclerosis. But the history was that of a disease with an acute onset which lasted three weeks, and leaves the question of meningitis unanswered. Stieglitz records 3 cases, nine, eleven, and fifteen respectively. All three are doubtful from the description of the clinical picture; but in fairness it must be said that the diagnosis of multiple sclerosis was definite in that author's mind.

Schuler, mentioned by Nolda, reported a case of multiple sclerosis in a child, which was proved by autopsy. Rauschburg (1909) reported the case of a boy of seven who had partial paraplegia, intention tremor and slight speech disturbance. The disease began at one and one-half years of age, there was no history of previous illness and no hereditary factor. Although the case is not proved pathologically the diagnosis seems not improbable. Schlesinger (1909) described the case of a boy whose history, signs and symptoms pointed to a subacute process. The diagnosis of disseminated sclerosis was made because of the multiplicity of symptoms and the eye signs (optic atrophy). Encephalomyelitis was considered as a possible cause. The patient died and came to autopsy. Macroscopic and microscopic study confirmed the diagnosis of subacute multiple sclerosis.

In my own records taken from Mt. Sinai Hospital there is the history of a boy of ten who was normal up to the age of six and a half when he developed sudden paralysis of the right arm and later of both legs. There were no fever, headache, vomiting or other symptoms of acute illness. He had absent abdominals, a left Babinski and normal electrical reactions. He recovered from this attack and within the next three years had 4 others in which he showed ataxia, tremor, absent abdominals, the Babinski sign and laughing spells. Fairly good recovery followed each attack. The remissions together with the signs and symptoms seemed to justify the diagnosis of multiple sclerosis. In the Montefiore Hospital records, there is the history of a girl of eighteen whose illness began at the age of eight with difficulty in walking, weakness of the hands, incontinence of urine. Physical examination showed a spastic gait, tremor of both

hands, lively deep reflexes, bilateral clonus and Babinski and absent abdominals. Clinically there seems to have been no question as to the diagnosis of multiple sclerosis. Another case is that of a young woman of twenty-seven, the onset of whose illness dates back definitely to the age of thirteen. Physical examination showed nystagmus, intention tremor, absent abdominals, bilateral Babinski and pallor of the optic discs.*

There are 8 other cases in my records which began respectively at fourteen, fifteen, sixteen and seventeen. The histories of 3 of these are not reliable and the diagnoses are doubtful. There remain 5 cases, 1 of fourteen, 2 of sixteen and 2 of seventeen in whom the clinical diagnosis of multiple sclerosis was not to be questioned. As the period of childhood cannot be stretched beyond fifteen years, there remains only 1 other case of fourteen which may be included in the group of early multiple sclerosis. We have then 4 cases occurring in children out of a total of 197, or 2 per cent.

From the above study one may draw a fairly definite conclusion as to the existence of multiple sclerosis in children. The vast majority of cases stand unproved. In many instances the diagnoses were erroneous; yet it is difficult to explain why careful observers should have attempted to prove the existence of infantile multiple sclerosis by means of doubtful cases. Many were very likely atypical, but could be better explained by the diagnosis of congenital disseminated lues, various traumatic birth palsies, spastic diplegias, Little's or Foerster's types, family spastic paralysis, Friedreich's disease, tumors of the brain, hysteria, encephalomyelitis and cerebral sclerosis. Nevertheless, a few authentic cases remain. Those have been proven both clinically and pathologically to have been multiple sclerosis. Its existence, therefore, in children, while very rare and in need of scrutiny, cannot be doubted.

Familial, Congenital and Hereditary Multiple Sclerosis.—The question of familial, congenital and hereditary influence in disease in general and multiple sclerosis in particular is in need of strict definition. Loose interpretation of the meaning

* These cases will be reported at greater length in a special paper on Multiple Sclerosis in Children.

of those terms is responsible for many broad and erroneous conclusions. To speak of a congenital or hereditary predisposition, while possibly permissible, is not very enlightening. That a disease be considered congenital one must prove its existence in the parent at the time of, or subsequent to, impregnation, that it was transmitted to the germ plasm or embryo or fetus in utero and that it was present in the child at birth, although it need not have manifested itself immediately afterward. Again, to speak of heredity one must show that the disease existed in some of the antecedents and collaterals, that it manifested itself in the descendants and that it affected the various individuals with a fair degree of consistency or regularity. True Mendelianism will not accept, of course, an interpretation of heredity which does not conform to its laws. Further, one isolated instance cannot be accepted as proof of a general conclusion for the reason that there are too many possibilities by the law of chance, among so many hundreds and thousands of cases, that the disease may appear hereditary. The same may be said, although with less emphasis, about familial influence in disease.

There are moreover, two distinct notions of hereditary or familial influence in nervous diseases which are current in medical literature. The older, which is gradually being discarded, is to consider any nervous disease in the family as a possible influence on or cause of any other nervous disease. Thus it is not unusual to find epilepsy, alcoholism, insanity, hysteria, neurasthenia, fright and exhaustion mentioned as possible hereditary(!) causes of multiple sclerosis. The more recent view, of course, and perhaps sounder, is to accept only the given disease in the consideration of familial, hereditary and congenital factors.

Whether or not these factors are operating in multiple sclerosis cannot be definitely answered, but there are numerous instances where the disease occurred in parent and offspring. Among my own records there is one instance in nearly 200 cases. It is that of a woman of fifty-five who has multiple sclerosis, which began at fifty, whose son died from the same disease at twenty-two. This instance cannot be looked upon as congenital for the reason that the mother developed the disease twenty years after the birth of her son.

Eichhorst cites a case in which there may have been a congenital factor. A woman who had typical multiple sclerosis for two years gave birth to a child who developed the disease. The mother died at forty-two and the child at nine. Autopsy showed a typical sclerosis of the cord. Two children born before their mother developed the disease did not have it. Pelizaus reports an hereditary disease which occurred in 3 generations of males and was transmitted through the mother. It showed itself in 1 son, 3 grandsons and 1 great-grandson. Pelizaus believes that the disease was multiple sclerosis. The clinical picture was the same in all cases and came on at the same age in all. There was bilateral nystagmus, speech disturbances, spastic paraplegia without atrophy, increased reflexes, intact sensibility and moderate dementia. Although perusal of the clinical histories does not altogether convince one, Pelizaus seems to be of the opinion that all were cases of multiple sclerosis.

Klausner reports 2 cases in a brother and sister of twenty-five and twenty-seven years respectively. Weisenburg reports 2 cases in a brother and sister, whom he personally observed, and a 3rd member in the same family is said to have suffered from the disease. The brother developed the disease at fifteen and the sister at four. The family was English. Reynolds reports 3 cases, the 2d, 4th and 6th in 1 family, a sister and 2 brothers of thirty-three, thirty and twenty-seven years respectively. The parents were psychopathic. He further quotes another English family in whom the 1st and 3rd developed multiple sclerosis at twenty-five and fifteen respectively. Frerichs and Erb (quoted by Borst) mention the disease in siblings, Totzke in 2 sisters of eleven and fourteen years and Elta in mother and son. Among the records of the Montefiore Hospital are found 2 instances where the disease occurred in a brother and sister.

Merzbacher reports the case of a family with 11 members in whom a disease very much like multiple sclerosis developed in the fourth month of the lives of the individuals. The patients had nystagmus and tremor of the head. One came to autopsy at the age of twenty and on microscopic examination the myelin sheaths were found totally absent. No extensive description is given. Coriat reports a peculiar

form of family nervous disease resembling multiple sclerosis occurring in children. There were 4 patients of Russian (Hebrew) parentage, 2 of them being brother and sister, a boy of eighteen and a girl of eight years.

From the foregoing cases it may be seen that the evidence is not very conclusive. Eichhorst's isolated instance may be looked upon as possibly illustrating congenital transmission. The numerous other instances where the disease occurred in more than 1 member of a family or in parent and offspring cannot be considered, in view of its comparative prevalence, as absolute proof of familial and hereditary forms of multiple sclerosis. In this connection, too, one need consider the relation of the experimental investigations as to the etiology of multiple sclerosis. This disease has come to be looked upon as the result of a subacute or chronic infection and the gliosis has been interpreted as a reaction to inflammation. Obviously it makes some difference so far as this discussion is concerned whether the inevitable focal infection plays any causative part or a spirochete is the etiological factor or "abiotrophy" and "systemic degeneration" are invoked to explain the genesis of the disease. It is quite possible however that the discovery of the causative agent of multiple sclerosis will clear up the question of the existence of familial, hereditary and congenital types.

The following questions submitted to Dr. Wechsler before the Commission, together with the answers to them, are here reported verbatim.

Dr. Dana: Do you not think this is the proper time to start quite a new study of statistics, not extending back further than four or five years. It seems to me we have been looking at it from quite a different point of view; we have recognized symptoms that were not recognized four or five years ago; in fact, you referred to that yourself. I should think if you wanted to take the statistics of the present day and go over them alone, the conclusions might be a little different from those at which you have arrived.

Dr. Wechsler: I believe that the 200 cases studied, are rather different from those that are found in the literature, and I think you are perfectly right in making the statement.

Dr. Taylor: Is it not a fact, that in the foreign statistics, early statistics, the ratios and percentages were drawn simply from the

organic cases, whereas in this country they were drawn from the organic plus the functional cases? Am I correct in that?

Dr. Wechsler: Most of the cases, as you say, were drawn from general neurological clinics, both organic and functional, both in Europe as well as in this country; but Bramwell is the only man who gave 2 distinct figures, and I have tried to divide the figures wherever it was possible.

Multiple Sclerosis and the Methods of Ecology

Charles L. Dana, M. D.

1. Ecology is the science of the relation of a living organism to its environment. It deals with such organisms much as sociology deals with mankind and is to be learned rather in the field than in the classroom.

It was originally a term used in connection with plant life and was linked up with botany. But the science has now been applied to animal life, and there are animal ecologists as well as plant ecologists.

2. Ecology has been taken up by entomologists and applied to insect and parasitic life in relation to human or other environment. There are, in other words, entomological ecologists. Since bacteria, pathogenic to man, are also really parasites, it is quite proper to speak of a bacterial ecology as one phase of animal or zoological ecology.

I am assuming that there is an infecting organism at the bottom of the multiple sclerosis lesions. I even assume it is an animal type, i.e., some variant of spirochaetae, hence I place the problem of multiple sclerosis in the domain of animal ecology.

Such an ecology would study the relations of this living microbic animal to its environment. If this assumption is wrong, and the lesion of multiple sclerosis is not due to a living plant or animal, but to some kind of poison or irritant or embryonic defect, the ecologist may study the living animal, man, with reference to his environment, using the same procedures.

Ecology was originally a field and not a classroom study. It is such now; but in animal ecology and especially in bacterial ecology as applied to man and to disease, the laboratory must be utilized.

3. The ecologists describe and study living things in "groups" or "formations," e.g., they study a forest, instead of a tree; the fish of a special lake region, instead of an individual fish; a tribe of men, instead of an individual.

Those persons all over the world who are suffering from multiple sclerosis form a special kind of zoological group which may be studied as a unit, or "formation." Ecology deals with internal factors, i.e., the structure and function of this formation, and with the external factors acting upon it. These latter are the environmental stimuli, some of which act during prenatal life. It therefore inquires into these prenatal conditions and the birth and development of the child.

It considers also the geographical, climatic and racial distribution; the mode of life, occupations, habits and morphology of the people affected; the diseases prevalent in the areas where the multiple sclerosis prevails; the existence and distribution of multiple sclerosis in other animals than man. We search for and study an area and a race where immunity exists, as perhaps in Japan.

We study the diseases which initiate or complicate or prevent it.

4. Ecology gives emphasis to the fact that a living animal-group depends for its existence upon a proper environment, and that the causative factors or stimuli in the environment are linked together so that one may need to remove only one factor in the chain to destroy this animal group. For example, agricultural plant life is dependent on many factors of climate, soil, moisture etc., but all human agriculture would cease if there were no birds; and some of it if there were no angle worms.

The existence of a peculiar type of men, the Polar Esquimaux, depends upon many factors, but a writer in the journal, *Ecology*, has recently shown that these Esquimaux would disappear if the water of the Arctic Ocean were not rich in CO_2. This is a fundamental link in the causation and existence of the tribe. We might say there would be no multiple sclerosis if we could safely skip or bridge over the years from ten to forty! It is hoped that we may find other causal factors more easily controlled.

5. In following up this environmental study, we may adopt the use of the *ecological quadrat* system. A certain area of country, a state, or group of states is studied, or we would say "surveyed" *in re* multiple sclerosis, this survey is repeated each year; the number, distribution, and character of the multiple sclerosis cases are noted. Various quadrats are assigned to investigators, and thus in time the effect of environment on the disease is obtained, and the facts of distribution and the increase or decrease of the disease established.—A quadrat involving the Atlantic Coast, the Great Lakes, the Rocky Mountain plateau, the Pacific Coast, might be established.

6. Having finished a study of the extra-human environment, we study the bodily condition of the patients who have multiple sclerosis, i.e., the immediate somatic environment.

We search for all the physical and physiological metabolic and chemical factors connected with the body that environs the multiple sclerosis nodules. Under this head come: Family characters, age, sex, race, temperament, endocrin and metabolic balance, diet, etc.

With regard to this body environment, we ask if it is modified favorably by other diseases. Is there any disease which leads to immunity or to susceptibility? A study should be made of all the preceding infections which the patients have had. It might be found that the disease never occurred in a person who had, e.g., arrested tuberculosis, or that the disease increased with reduction of acute communicable disease, or is promoted by ancestral lues. It seems to me that multiple sclerosis is relatively rare in the tuberculous, and I cannot find it in the mental defectives, nor much of it in the strictly laboring classes, or muscle workers.

Morphologists seem to be coming to the view that there are two types of human beings, the linear or dolichocephalic type, which is thin, has rather vertical ribs and stomach, short small intestine, a high basal metabolism, very slight variability of weight, and is mentally nervous, but self-controlled.

The other type is broadly built, is brachycephalic, tends to stoutness, variability in weight and is emotional. I give the features only in outline.

I should say that patients with multiple sclerosis are more of the linear dolichocephalic type. I have never seen multiple sclerosis in a fat man or woman even when long bedridden.

7. We come finally to study immediate nervous tissue environment of the multiple sclerosis nodules, looking for the forces which make the nodules group themselves as they do, in the spinal cord and brain.

This forms a study of the special tissue habitat of the object and involves a consideration of the vascular supply and the bio-chemistry of the parts chosen for the development of the nodule, in order to find out why it selects the nervous system and why the pyramidal tracts and synergic centers and not the afferent or sensory or peripheral motor neurons. They must grow in their chosen places because the "climate" of the cerebrospinal system suits them.

8. I have discussed the three enfolding environments of the animal X in sclerosis disseminata—the extra human world, the human body and the nervous tissue. Ecology applies in all these relationships, but it is particularly the extra-human field which makes appeal and offers opportunity. Ecology has been, as I have said, essentially a field-work science. I have experimented a little in this line.

Dr. Mary M. Sturgis, who has had training with Dr. C. B. Davenport, has taken 10 cases of multiple sclerosis, observed and diagnosed at the Cornell Clinic and Bellevue Hospital Neurological service. She has visited the homes of these patients, seen them and their families and obtained details of the life of the patient and family and the incidence and development of the disease. The study is not complete, but it already contributes definitely some facts regarding the causes and progress of the malady in the patients thus studied.

9. I am quite aware that many of the lines of inquiry suggested by ecological methods have been tried out under the head of etiology and pathogenesis. But there has been no intensive and persistent research in many of the directions here suggested. After all, our science does not progress by simply observing, recording and classifying. There must be special skill and special ways of making research successful. There is a technique which amounts to an art in becoming

fruitfully scientific. In calling attention to ecological methods, I have thought I should be able to emphasize the importance of long and patient field study.

It will be seen that this paper is not so much a contribution as a series of suggestions and a questionnaire. I am impressed with the fact that some of the neurological problems are enormously difficult and will not be solved unless we adopt all possible methods of approach. If we discover the pathogenic agent, and secure a serum or vaccine that protects or cures, our labors will be enormously lightened, but not finished. They will not be finished till we learn not only how to cure multiple sclerosis, but how to rid humanity of this minor but dreadful scourge, before which we have so far been helpless.

Although life is short and neurological ecology long, I hope we shall take up at least some of its field methods, enlarge our vision and pursue our task with pertinacity and zeal. I have asked my field worker to keep at it for a year.

The Conclusions of the Commission

1. The age of persons suffering from multiple sclerosis ranges chiefly from twenty to forty, but the disease may occur as early as the tenth or as late as the sixtieth year.

2. The disease occurs more often in males than females in the ratio of about 3 to 2; and makes up about 1 to 2 per cent of the organic diseases of the nervous system including those due to syphilis.

3. The duration of the disease averages about eight years but may run less than a year or more than thirty years.

4. It occurs in persons doing skilled manual work more often than in ordinary laborers or in brain workers.

5. In the Unites States it seems to occur more in the region of the Great Lakes—at least among young males, while in Europe it prevails more in Northern parts than in Italy and about the Mediterranean Sea.

6. It is not a familial disease, and is not inherited, there being rare and doubtful exceptions; but in the ancestry there is often evidence of a neuropathic stock.

7. Acute infections may immediately precede the disease in a small percentage (10 or 12 per cent) and it occurs no more frequently in persons who have had the usual children's infectious fevers than in those who have not had them (Barker).

8. It is not caused by syphilis.

9. In a small percentage of cases the disease appears to be excited by trauma, but trauma cannot itself cause the disease, and only may apparently awaken a disease process already potentially existent.

10. Further laboratory studies and the use of prolonged and intensive field work including some of the methods suggested by ecology are necessary to give us a knowledge of the real cause of multiple sclerosis, which cause we do not now know.

CHAPTER II

General and Special Symptomatology

Section I

The General Symptoms of Multiple Sclerosis and the Mode of Development of the Symptoms of Multiple Sclerosis

This section deals with the symptomatology of multiple sclerosis both in its general manifestations and also in the mode of development of symptoms of multiple sclerosis especially in the early stages.

The general symptomatology of the disease is presented by Dr. Bernard Sachs of New York City, in association with Dr. Emanuel D. Friedman of New York City; the mode of development of symptoms of multiple sclerosis, especially in the early stages, is considered by Dr. William B. Cadwalader and Dr. John W. McConnell of Philadelphia.

General Symptomatology of Multiple Sclerosis

Bernard Sachs, M. D. and Emanuel D. Friedman, M. D.

Hitherto, there has been a wide divergence of opinion. Some have thought the disease rare. Others that it is nearly as frequent as tabes. In this country the disease was at one time thought to be infrequent. In Japan it is said to be practically unknown. On the other hand, Marburg claimed that next to lues it was the most common organic disease of the nervous system, and Stieffler has laid especial emphasis on the frequent occurrence of multiple sclerosis among German soldiers during the War. One group of authors has claimed that it is post-infectious—possibly a form of encephalomyelitis (Marie). Others have contended it is more often endogenous and degenerative (Strümpell and Mueller), or that it is endogenous and toxic (Oppenheim).*

* A history of Trauma was noted in only 4 of our cases.

Some of us were firmly convinced that multiple sclerosis is one of the few positively nonsyphilitic diseases of the central nervous system; while others again, including Spiller, feel that syphilis may be an important factor in the causation of the disease.

Many observers in this country and Europe, more particularly in France, will not make the diagnosis of multiple sclerosis unless there be present the classical triad of symptoms, namely, nystagmus, intention tremor and scanning speech; while others, like ourselves, venture to diagnosticate the disease in the presence of another series of symptoms, although one or two of the famous Charcot triad, developed and emphasized by Charcot and his followers, may be absent. As in tabes dorsalis, the earlier concepts of multiple sclerosis were based upon the full-fledged chronic forms of the disease, and as such the older clinical studies were keen and discriminating. The present-day views, at least those which we hope to prove acceptable, are based upon the attempt to recognize the disease in its earliest stages.

TABLE I

SIGNS AND SYMPTOMS OF MULTIPLE SCLEROSIS IN THE ORDER OF THEIR DIAGNOSTIC IMPORTANCE BASED UPON THE STUDY OF 141 CASES

	Per cent
1. Easy fatigue, weakness and stiffness of one or both upper or lower extremities culminating in spastic paraplegia	81.7
associated with	
(*a*) Increase of deep reflexes	90.0
(*b*) Positive Babinski sign	78.3
2. Nystagmus, generally horizontal, slight at the beginning, gradually becoming more marked	70.0
3. Ataxic tremor of upper extremities and tremor of the head	55.3
4. Marked diminution or loss of abdominal reflexes	83.7
5. Spastic ataxic or ataxic gait and station (including the Romberg symptom)	43.2
6. Scanning speech or some form of dysarthria	36.0
7. Pallor of optic discs, especially of the temporal halves	32.6
8. Disturbance in facial innervation, often very slight	32.6
Deviation of tongue	10.0
Disturbance of deglutition	3.5
9. Explosive laughter and emotional instability	17.0
10. Unusual remissions often leading to disappearance of symptoms	42.0

	Per cent
11. Transitory ocular palsies with diplopia	29.0
12. Vague objective and subjective sensory disturbances:	
(*a*) Objective (1) Posterior column disturbance	17.0
(2) Pain, touch and temperature disturbance.	16.3
(*b*) Subjective: Numbness, tingling and pain	30.0
13. Disturbance in vesical (not rectal) reflexes	40.0
(Hasty or delayed micturition); incontinence in 21 cases	14.0
14. Tenderness of the spine, chiefly mid-dorsal	12.0
15. Dizziness (vestibular vertigo)	8.25
16. Mental changes	15.6
17. Auditory nerve involvement	2.0

IMPORTANT NEGATIVE SIGNS AND SYMPTOMS

1. Pupils generally active with occasional hippus.
2. Biologic tests negative except for the occasional presence of globulin and slight increase in the number of cells in the spinal fluid in a few instances.
3. Colloidal gold curve reported as paretic by some writers. Not sufficiently studied in this series.

First, it is of special interest to note the gradual development of the weakness, as a rule in the lower extremities, in association with the increase of the deep reflexes.* The upper extremities are less frequently involved in the general loss of power, while a very slight ataxic tremor† often precedes by months the development of weakness or paralysis of the upper extremities and the upper extremity reflexes are increased at a very early day. Note also that in both the upper and lower extremities weakness or paralysis is associated with a very moderate degree of spasticity; not infrequently there is also in the early stages of the disease a very slight though distinct disturbance of sensation.‡

The fact that the disease patches occur at various levels in the pyramidal tracts and in the cerebellar pathways accounts for the character of the motor symptoms, and also for the easy division into special types in accordance with the topographical distribution of the lesions.

* In 115 cases the chief complaint was weakness and stiffness of one or both lower extremities.

† Cerebellar ataxia and adiadokokinesis were noted in 66 cases, showing the frequent involvement of cerebellar pathways.

‡ Astereognosis was noted in 5 cases, possibly accounting for the "loose arm" referred to by various writers.

If we choose, we may establish spinal (the tabic), bulbar, cerebral, hemiplegic, cerebellar types.

The disease process and the disease symptoms are widespread. Of the increase of the deep reflexes* little need be said, except that the increase is within moderate bounds—that it is generally equally and symmetrically distributed over the entire body, and that in many instances the jaw jerk is very active, as evidence that the sclerotic patches may be distributed throughout the length and breadth of the central nervous axis.

It is much more important to add a word regarding the diminution or loss of the abdominal reflexes. As a matter of fact this is the one symptom of importance that has been added to the symptomatology of multiple sclerosis within the last twenty years. We have been forced to attach great significance to it, yet it is only fair to state that some French authors like Marie and Sezary† are inclined to disregard the value of this reflex.

In any number of instances the absence of abdominal reflexes has helped us to suspect the presence of disseminated sclerosis early in the disease, the suspicion of the diagnosis having been confirmed by the subsequent course of the disease. But how can we account for the frequent loss of this cutaneous reflex? Except at the beginning of the disease, all abdominal reflexes seem to be equally affected. I find no other explanation except that in view of the extensive character of the disease, the reflex pathways with their cerebral connections, are certain to be hit somewhere by one or more of the sclerotic patches; and this view is substantiated by Monrad-Krohn, a Scandinavian writer, who in a recent and exhaustive monograph on the abdominal reflexes, holds that these reflexes are present in all healthy individuals with normal abdominal walls, and that there is a pathway connecting the spinal arc with the sensory-motor cortex.

So far as the speech disturbances are concerned, "scanning

* Ankle clonus was present in 61 cases; patellar clonus in 29 cases. The knee-jerks were diminished in 3 cases, and so were the Achilles reflexes (tabic type).

† Traité de Pathologie Médicale et de Thérapeutique Appliquée, Tome I, p. 338.

speech" does not tell the whole story. In addition to or instead of syllabic utterances we may have other forms of dysarthria. Speech may be purely tremulous or bulbar or cerebellar in character.

Ever since Uhthoff's day, the pallor of the temporal halves of the optic discs* has had great diagnostic value, and last but not least the unusual remissions of the disease often afford great difficulty in diagnosis. Every now and then men of experience begin to doubt the diagnosis because of the disappearance of many signs. The gait improves, the speech becomes less scanning, the contractures are partially relaxed, the ataxic tremor of the upper extremities may be far less pronounced. There is great subjective improvement reported by the patient, and the general progress is so marked that not infrequently hysteria or some functional form of disease is suspected.

The diagnosis of multiple sclerosis may safely be made if a number of the important symptoms enumerated in Table I are present, and if the disease runs a subacute or chronic course.

TABLE II

TOTAL NUMBER OF CASES STUDIED 141 (MALE CASES 77, FEMALE 64)
SYMPTOMS AND SIGNS ENUMERATED IN THE ORDER OF THE FREQUENCY OF THEIR OCCURRENCE

	Per cent
1. Spinal fluid was negative in 114 out of 122 cases studied	93.0
In 19 cases there were no spinal fluid studies.	
The blood Wassermann test was negative in all but one instance in which the outcome was three plus. In 5 cases there is no record of a blood Wassermann test. Spinal Wassermann test was negative in all the cases studied. In 3 cases the globulin in the spinal fluid was increased	2.1
In 8 cases the cell count was above normal, the figures being 12, 13, 16, 16, 20, 30, 40 cells respectively	6.8
2. Abdominal wall reflexes were markedly diminished or absent in 118 cases	83.7
3 The chief complaint in 115 cases was weakness and stiffness of one or both lower extremities	81.7
4. Nystagmus was present in 99 cases	70.0
It was chiefly horizontal.	

* Expert ocular examination revealed "blurring of the discs or mild optic neuritis" in 11 cases. Vision was found "impaired" in 25 cases without objective disc findings.

	Per cent
Horizontal and vertical in 17 cases	12.0
Horizontal and rotary in 3 cases	2.0
5. Babinski's sign was present bilaterally in 94 cases	67.0
Unilaterally in 16 cases	11.3
6. Tremor was present in the extremities alone in 78 cases	55.3
In 31 cases there was also tremor of the head	22.0
7. Ataxia and adiadokokinesis were present in 66 cases	47.0
8. Deep reflexes in the lower extremities were increased in 126 cases	90.0
Ankle clonus was present in 61 cases	43.0
Patellar clonus was present in 29 cases	20.5
In 3 instances the knee-jerks were diminished and in 3 cases the ankle-jerks were diminished (tabetic type).	
9. There was a history of 1 or more remissions in 59 cases	42.0
10. There were bladder symptoms in 57 cases	40.0
Urgency was present in 18 cases.	
Delay in starting urinary stream alone or in combination with urgency in 28 cases and incontinence in 21 cases.	
11. Speech was hesitant or otherwise disturbed in 51 cases	36.0
12. The gait was spastic in 43 cases	30.0
Spastic ataxic in 46 cases	32.6
Ataxic alone in 15 cases	10.6
13. In 46 cases there was evidence of facial weakness	32.6
The other cranial nerves were very much less involved.	
The tongue deviated to the right in 14 cases	10.0
There was difficulty in swallowing in 5 cases	3.5
Uvula was drawn to one side in 4 cases	2.8
The cochlear nerve was involved in 3 cases	2.0
In 2 cases the vestibular nerve showed no response to stimulation	1.4
Of the ocular muscles the internal rectus was involved 6 times	4.3
In 2 cases there was ptosis	1.4
In 3 cases the external rectus was involved	2.8
These last figures are rather interesting in view of the frequency of diplopia in multiple sclerosis.	
14. Temporal atrophy was noted in 46 cases	32.6
In 11 cases there was blurring of the discs or mild optic neuritis	7.8
Vision was impaired in 25 cases without objective disc findings	17.7
15. Sensory changes were both subjective and objective. Pain, numbness and tingling were noted in 43 cases	30.0
Objective disturbances in posterior column sensation were present in 24 cases	17.0
Mild changes in pain, temperature and touch perception were noted in 23 cases (among these were cases with hyperalgesic zones)	16.3

	Per cent
Astereognosis was noted in 5 cases	3.5
16. There was a history of diplopia in 31 cases	29.0
17. Cremasteric reflexes were diminished in 17 of the male cases	22.0
18. Mental changes were noted in 22 cases. They were largely those of mental infantilism and signs of neurosis or neurasthenia. One patient was in a State hospital with the diagnosis of dementia præcox. One patient showed the picture of Korsakoff's psychosis	15.8
19. 24 cases showed emotional instability with explosive laughter	17.0
7 cases showed defects of memory	5.0
20. Spinal tenderness was present in 17 cases	12.0
It was chiefly middorsal.	
21. In 14 cases there was a history of trauma	10.0
Two cases had shown symptoms of lead poisoning.	
One patient had suffered from wood alcohol poisoning.	
The disease followed operation in 2 instances and in 1 case it developed as a result of fright.	
22. Pupillary disturbances were noted rarely.	
Pupils were irregular in 6 cases	4.3
They were slightly sluggish to light in 12 cases	8.5
Ainsocoria was present in 16 cases	11.3
23. In 12 cases there was a history of marked dizziness	8.5
24. Disturbance of potency were noted in 6 cases	4.3
No disturbance in rectal control were seen in any of our cases.	

A study of the age incidence shows that 8 cases occurred during the second decade of life, 47 during the third, 53

TABLE III

COMPARATIVE INCIDENCE OF MULTIPLE SCLEROSIS AND LUES OF THE CENTRAL NERVOUS SYSTEM

At Montefiore Hospital for Chronic Diseases, 1914–21 Inclusive

	Cases
Multiple sclerosis	50
Lues of the central nervous system	167
(*a*) Cerebro-spinal lues	65
(*b*) Tabes	85
(*c*) General paresis	17

At Mt. Sinai Hospital, 1912–21 Inclusive

	Cases
Total admissions to the neurologic service	2,357
Multiple sclerosis	90 (3.8%)
Lues of the central nervous system	562 (23.8%)
(*a*) Cerebro-spinal lues	317
(*b*) Tabes	160
(*c*) General paresis	85

during the fourth, 25 during the fifth and 5 during the sixth. Most of the cases (100) occurred between the ages of twenty and forty.

The following questions submitted to Dr. Sachs before the Commission, together with the answers to them, are here reported verbatim.

Dr. Taylor: Regarding the abdominal reflexes, what is your personal experience regarding its loss under normal conditions?

Dr. Sachs: I think that we find it in all normal cases. I am in perfect agreement with that statement of Monrad-Crohn, who has written a monograph on this subject, that it is a reflex which is normally present; but you must remember that in persons who are obese, in women who have passed through the stage of pregnancy, it is a very difficult matter always to elicit it.

May I say one thing more about this reflex? The value of it is extremely great in this way: that if we find it associated in other conditions with other reflexes, for instance, in the ordinary case of hemiplegia, the absence of it on the hemiplegic side and the marked presence of it on the other is very characteristic. And the one thing that is said about the diminution of the abdominal reflex in multiple sclerosis is that it is almost uniformly symmetrically affected.

Dr. Patrick: Dr. Sachs spoke of the remissions; he did not say anything about acute exacerbations; whether they have been relatively frequent or rare, and whether in these acute exacerbations there is not a great increase in the lymphocytosis.

I should like to ask Dr. Sachs whether he has ever observed the Argyll-Robertson pupil in multiple sclerosis; also whether in cases of pallor of the optic discs the color fields have been taken, and whether there has been any enlargement of the blind spot?

Dr. Sachs: I thought I had stated that the acute exacerbations were just as important as are the remissions. I cannot say whether the acute exacerbations, in my experience, have followed almost invariably upon the remission.

I have not had occasion to examine all the cases so as to note whether there is an increase in cells in exacerbations; hence, I cannot make a positive statement, but I should think there would be.

As far as the Argyll-Robertson pupil is concerned, my feeling is that it occurs so rarely in any other condition except in one of the luetic degenerative diseases of the brain or cord, that I am willing to say that in multiple sclerosis it never occurs; in fact,

if I saw a case that I otherwise considered multiple sclerosis and found that that person had an Argyll-Robertson pupil, I should be greatly inclined, on account of that, to consider it out of the category of disseminated sclerosis.

The color fields have been taken, I believe, in some of our cases, but I have not any statistics on hand to make any definite statement regarding that, nor with regard to the enlargement of the blind spot. At present I have not at my command any special data on that point, but I may possibly be able to fill up that deficiency.

Dr. Strauss: I would like to ask Dr. Sachs one point regarding this statement of a slight increase in the number of cells. From your study of statistics, what is the amount of increase in the cells?

Is it not a fact that the increase of cells depends first upon what you regard as the normal number of cells in the spinal fluid, different authors taking different numbers as the normal; and second, upon the method used in counting and the time in which the cell count is made? After all these facts, may we not state that from the studies made on the spinal fluid, one can practically disregard the cell count in making a diagnosis of multiple sclerosis?

Dr. Sachs: Dr. Friedman has just handed me our detailed figures here. We found in 8 cases the cell count was above normal, the figures being 12, 13, 16, 16, 20, 30 and 40 cells, respectively; so that we regarded anything above, I should say, 10 or 12 cells, as absolutely abnormal. Whenever the cell count is higher than that, of course, there is the suspicion, I think, of some acute process, whether specific or not, which should be entertained. If all the other signs point to the probability of specific infection, the increased cell count would corroborate that diagnosis.

I have put that under the "Important Negative Signs" simply because of the value of having a very low cell count in cases suspected of being cases of disseminated sclerosis, a very important diagnostic factor.

Dr. Hunt: Is there any symptom in multiple sclerosis which one might regard as more or less pathognomonic of the disease—one or more symptoms?

Dr. Sachs: I am very glad to answer that question. That is just what I have been trying to get away from. There is no one symptom, nor are there any two symptoms that I would consider pathognomonic of the disease. You cannot base a diagnosis of this disease on any one or two symptoms. No doubt many of the old cases of primary or lateral sclerosis come now under the heading of disseminated sclerosis.

If you were absolutely to compel me to say which signs have been most helpful to me in making a diagnosis of disseminated

sclerosis, I would say that a slight nystagmus, a diminution of abdominal reflex, and a moderate spastic paraplegia—that group of symptoms is to me much more characteristic in the larger number of cases of disseminated sclerosis than is Charcot's triad. We see so many of these cases that have not a trace of speech disturbance or the slightest intention tremor for at least five or ten years during the disease. I should prefer not to state this as another triad. I do not wish to substitute that; it is just that which I am trying to avoid. The disease process is so widespread, the number of symptoms that arise is so different in the various cases, that to the best of my knowledge, one should bear in mind at this point at least the first 9 groups of symptoms and try to make the diagnosis, if any number of these are present. But in a certain case there may be only a spastic paraplegia and absent abdominal reflexes, with neither nystagmus nor scanning speech; slight disturbance of sensation or slight disturbance of the vesical reflex, or a combination of these symptoms. If, in addition, there is pallor of the optic discs (to which we attach great importance, when it does occur), I should say the patient has multiple sclerosis.

Dr. Hunt: For example, take the tendency to remissions: Might not that be regarded as a fairly characteristic symptom of the disease, clinically, when it is well marked? Is there any other organic disease in which it occurs in that way?

Dr. Sachs: Yes, I think in spinal syphilis it occurs at times even more markedly, although, I think that I have seen just as marked remissions in multiple sclerosis as in spinal syphilis.

Remissions and exacerbations are all very well in the course of a disease, but they have not, after all, the great diagnostic importance which other very positive signs have, because so many things improve and then get worse; and that is practically all that a remission, clinically, appears to be. I do think that spinal syphilis surely has just as marked remissions. For those who have not seen a large series of these cases, it would be surprising to them to see the very marked remission that does occur in disseminated sclerosis. That was a point years and years ago on which Oppenheim chastised me in an article, for not having paid sufficient attention to that fact, and I have kept it in mind ever since, as I take any lessons of that sort very much to heart.

The remissions are very marked. Only recently, I might say, I had occasion, with one of my own associates, to see a case of unquestionable disseminated sclerosis. All the symptoms were present—the intention tremor occurring even in that case, the scanning speech, the spastic gait. The improvement was so marked that even the associate, who has been interested in this work with

the other members of the group, felt that the case might after all be a hysteria. It surely is not a hysteria!

I should like to add that I have not gone into the differential diagnosis. I know that everyone of you should be able to differentiate paralysis agitans and tumor of the brain and tumor of the spinal cord from these cases of disseminated sclerosis. It is curious to see that in the French and German literature great stress is laid upon the differential diagnosis between disseminated sclerosis and hysteria. That diagnosis does not play any great importance in our American experience, probably due to the fact that we do not often see the same type of hysteria as is seen in all the continental countries. On the whole, hysteria is one of the rarest diagnoses we make, and the differential diagnosis between disseminated sclerosis and hysteria has not been one that has troubled us in the least.

I should like to encourage you to get away from the idea that you may have a triad of symptoms. You may have a combination of any of the important symptoms that we clinically recognize as disseminated sclerosis.

Dr. Hunt: It has been held that the insignificance of sensory disturbances in contrast to the very marked paralyses and spasticities is rather characteristic of the disease in its more advanced stages. Would you regard that as characteristic or more or less pathognomonic?

Dr. Sachs: I think that is a position that is well taken. We have been struck by the frequent occurrence, just as I have put it, of vague objective and subjective sensory disturbances, not such as one would see, for instance, in a distinct myelitis, but in an extremely vague character, particularly objectively.

In some of the private patients whom I have seen, the very first symptom of which the patient has complained, has been a paraplegia of the upper extremities. If this symptom is in combination with the loss of the abdominal reflex, I suspect disseminated sclerosis.

I wish to refer to a very curious experience that occurred within the last month or so at the hospital. A patient definitely known to be a case of epidemic encephalitis, about three months after the initial infection of encephalitis, developed a symptom group that was absolutely that of a disseminated sclerosis.

Dr. Tilney: Did convulsive attacks make any showing at all in the series of cases, especially in those with mental changes, sufficient to get a percentage representation in your chart?

Dr. Sachs: Apparently not. Do you happen to remember that, Dr. Friedman?

Dr. Friedman: The only case of ours that had had convulsions was 1 case which at post mortem showed a subdural hemorrhage over the motor area.

Dr. Sachs: If that patient, who was otherwise in good condition, had had all the symptoms of disseminated sclerosis, and had developed a convulsive seizure, I would be suspicious of some complicating disease.

Dr. Barker: First, Dr. Sachs has made no mention of weakness of the abdominal muscles as a sign in this disease. I have been accustomed to ask the patient, when in the recumbent position, to fold the arms and to sit up without using the arms as support, so as to find out if the abdominal muscles are weak.

In the second place, as to the differentiation between hysteria and multiple sclerosis, I think some of us have had a little more difficulty than Dr. Sachs has intimated. I have a case under observation now who has difficulty in standing and walking, recurring difficulty in vision, a little disturbance in speech, abdominal reflexes sometimes present and sometimes hard to elicit, slight exaggeration of the deep reflexes; no Babinski. It has been a question in the minds of those who have seen that case as to whether it was multiple sclerosis or a functional nervous disorder.

The third point: Dr. Sachs seems to make the diagnosis very often of lues, with a negative Wassermann in the blood and in the spinal fluid. I would like to ask if he thinks the cases with repeated negative Wassermanns in the blood and cerebrospinal fluid could be cerebrospinal lues?

The fourth point: Does he attach much significance to the age of onset in differential diagnosis? In other words, especially in patients where the onset is after forty years of age, would he hesitate to make the diagnosis of multiple sclerosis?

The fifth point: Whether or not it is desirable to have a pathological group that we call multiple encephalomyelitis, without going any further, when we have difficulty in deciding whether a patient has multiple sclerosis or spinal lues or encephalitis? Is it not wise, perhaps, to have a vaguer syndrome that indicates multiple lesions of which we cannot determine the nature? In other words, make a localizing diagnosis but without definitely deciding as to the nature of the disease.

Dr. Sachs: I will try to do my best, Dr. Barker.

First of all, about abdominal weakness. I have no doubt you have tried these abdominal "stunts," but I must confess that we have not; I do not think we have tested out that special sign, but it seems to me there is so much difficulty in performing the little "stunt" you mentioned, even normally, that it is far from easy to evaluate such a weakness.

As far as hysteria is concerned, I really feel that while, of course, there may be cases in which there is some difficulty at the beginning, the difficulty is not apt to be a lasting one. I would not make the diagnosis of hysteria in a case in which there was any doubt in my mind as to whether it was a hysteria or a multiple sclerosis, unless there were some absolutely definite signs of major hysteria, such as contracted visual fields, absolute regional hemianesthesia, and a variability in the symptoms which is perhaps, after all, different from the variability in the symptoms in sclerosis. In sclerosis the variability in symptoms is a periodic one. I think in that way there would be a difference between the condition that you would find in hysteria and in multiple sclerosis.

There is one other group of cases in which the difficulty is really very great; for instance, the case of a piano teacher, a young woman of about twenty-five, who complained of fatigue and of not being able to give her lessons; she was a little depressed, even morbid over it. She felt she was not going to be able to follow out her profession, and so on. I thought this was in her case purely what at that time we called hysterical. Today we would probably speak of it as a psychotic condition, associated with her general neurotic make-up. But this same woman, in the course of a few months developed paraplegic weaknesses; and they were so vague I could not make much of it. She had been in a family, I had known, in which she was always spoken of as a highly neurotic individual, and the entire condition was taken rather lightly and was supposed to be one of her hysterical manifestations.

But, in a very short time, she began to develop a very marked ataxic tremor, which later developed into a marked intention tremor. Several months later she developed a nystagmus, and before long it was proven to be a typical case of disseminated sclerosis.

I have no doubt there will be difficulties at times in making a diagnosis, but I always claim for this disease, as for many other diseases (there are any number of diseases in which one cannot make a diagnosis on the first examination), that one can only hope to reach results after weeks and months of observation.

As far as the biological tests are concerned, perhaps I take a rather extreme view of the matter. I never allow biologic tests largely to influence diagnosis. If I make up my mind on clinical grounds that a case is multiple sclerosis, I am willing to have the laboratory corroborate that diagnosis, but I will not allow the negative findings to upset the positive diagnosis. I still maintain that there may be lues in spite of negative findings.

Hence, to my mind, at the present day, after all that I have seen of multiple sclerosis, of tabes and everything else, an immobile

pupil means ten times more to me than any biological finding. While I am inclined to respect positive findings and I also believe that the laboratory is always reliable, although not infallible, I only accept it as corroboration, unless the symptoms are positive; then, of course, if the examiner is a competent man, he cannot get away from it; nevertheless, I would not allow negative findings to upset the diagnosis.

As for the age of onset, I happen to have talked that point over with Dr. Friedman this morning and I told him that I really feel that, while the majority of the cases come on after twenty years of age, or at least we see them after twenty, we do not know how long the disease has been active in any case before we have had occasion to see it or before we are ready to make a diagnosis. Cases after forty years of age are, on the whole, rare and should make one, I think, rather suspicious that they may not be cases of typical multiple sclerosis, but that they may be spinal syphilis.

The last question that Dr. Barker asked, has also interested me, and I think I should put it this way: We are constantly in a state of flux, regarding our clinical designations and the corresponding pathological changes that go with those clinical designations. We have established a group of symptoms which we think is safe in the majority of cases, under the conditions I have mentioned so often, so as to make the diagnosis of multiple sclerosis; but whether this same group may not occasionally represent some other pathological process I am perfectly willing to believe, in fact, I think that is probably the case; and our recent experience is tending that way. I have no doubt that it would be very difficult in some cases to say whether the case is one of a disseminated, myelitic or encephalitic disturbance, or whether it is a case of disseminated sclerosis; and from the clinical experience we have had, I am not at all certain that the myelitic disturbances, or the early vascular disturbances even preceding general myelitic disturbances, may not be an essential preliminary in the development of the sclerotic patches.

The difficulty which Dr. Barker has mentioned is rather interesting and has evidently struck European observers. During a visit in Europe last summer, it was interesting to note that in Marie's clinic definite diagnoses are very rarely made. They will speak of the sensory motor complex and the cerebellar complex, and they mention those pathway groupings of symptoms very much more frequently than they mention definite diseases. They are very apt to speak simply of cerebellar groupings, of pontile cerebellar groupings, of ophthalmocortical groupings, without in every case making a definite diagnosis.

Dr. Starr: I would like to ask in what percentage of persons were abdominal reflexes absent? I ask it because Dr. Sachs has laid special stress on the absence of abdominal reflexes in this disease. Judging from a considerable experience, I am sure there are quite a number of persons in the world suffering from various diseases, or from no disease whatever, in whom abdominal reflexes are absent, or rather, whose reflexes I have been unable to elicit. We know that certain persons have no knee-jerks; that those who have had diphtheria have no knee-jerks for many years afterward. With this thought in mind, a pertinent question is: Is there a certain percentage of persons in the community who have no abdominal reflex?

Dr. Sachs: I am inclined to answer, in reply to Dr. Starr, that it is true of the abdominal reflexes, as it is true of the knee-jerks, that no normal individual should be without them, and if they are absent in a person whom you consider otherwise healthy, I think you would have to go back into that person's history and find out some other reason for their absence. I do think it is one of the symptoms which is normally present in the normal individual.

Monrad-Krohn comes to the conclusion that the reflexes are present in all healthy individuals with normal abdominal walls. Of course, after a person has had an appendicectomy or some laparotomy has been done, or after pregnancy, the constitution of the abdominal walls may be such that you cannot elicit the abdominal reflex; but I think it is a reflex which is present in all normal individuals.

Dr. Prince: I would like to ask a question on which Dr. Sachs has already given us some information. How far advanced have you seen the disease and yet have seen decided remissions of the symptoms occur?

Dr. Sachs: In my own experience, the remissions, I should say, occur within the first five years of the disease, and my interpretation of that is simply this—and I base it upon some of the more recent pathological specimens I have seen at the early stages: that once the sclerotic patches are widely and largely distributed, I dare say a period of remission is practically impossible, but it is in the earlier stages, say the first five years—I do not want to be too definite about that—there may be some remissions even within the first eight or ten years, but I have seen them within five years of the time that I have made the diagnosis of disseminated sclerosis myself in undoubted cases; up to a period of about five years, but after that I do not think they occur very often. I think some of the gentlemen who are familiar with the material of the Montefiore Home, might state whether they have observed any remission in

their cases at the Montefiore Hospital. My impression is that it is at the Montefiore Hospital where the patients are taken care of when they have once reached a spastic or paralytic stage that remissions are almost unknown.

Dr. Prince: I meant how far advanced, not from the point of view of chronology or from the point of view of symptomatology, but from the development of nystagmus. You spoke of a case being very well advanced a moment ago.

Dr. Sachs: I meant that the symptoms were very far advanced. This patient, to whom I referred, had a very marked spastic gait; the spasticity had disappeared so that he could walk without his stick. Formerly it had been necessary for him to use a stick in walking. His nystagmus was a little less. The speech in this case I know improved so distinctly that the patient thought he was just about as well as he ever had been; and yet, when the period of remission was over, the gait became very spastic, the scanning speech, the syllabic utterance, became more marked, and the whole disease has progressed. In that case I should say the whole disease could not have lasted more than about four or five years from its very inception, but I would be glad, Dr. Timme to know, and I think all the members might be interested to know, whether anyone at any chronic hospital, either here or elsewhere, has seen a remission in a very chronic case. It seems to me that some of these Philadelphia gentlemen who have seen some of these cases might give us some information on that.

Personally, I have not seen any remission in any of the chronic cases.

Dr. Timme: If any of the gentlemen present have a contribution to make, in response to Dr. Sachs' request, we should be very glad to have them hand it in in written form to Dr. Brown, and we should be glad to include that in the transactions.

I should like to ask Dr. Friedman, who has been associated with Dr. Sachs, to add to the presentation, if he so desires.

Dr. Friedman: I don't think there is very much to add to what Dr. Sachs has said.

I might answer this last question first by saying that we have in our records cases that have had paraplegias which have been transitory. Of course, we found in all those cases that had the disease picture well established that in the course of the disease some additional symptoms will be added. Besides the old lesions, one always finds additional new, fresh foci.

It might be worth while making some additional comments on the findings noted on the chart. Multiple sclerosis, according to our modern notions of the disease, attacks chiefly the pyramidal

tracts and the cerebellar pathways. In view of the extreme length and complexity of these pathways, foci lodged anywhere within their course would interfere with function and thus produce symptoms referable to those pathways.

Dr. Sachs has already referred to the work of Monrad-Krohn on the abdominal wall reflexes. He postulated a cortical arc in addition to the spinal arc, extending practically to the sensori-motor cortex, and in view of the length of this pathway, one can readily see why the abdominal wall reflexes should be diminished or absent.

With reference to the disturbances in facial innervation, these are usually of the upper motor neuron type, although in two or three of our cases it was of the peripheral variety.

With regard to the transitory ocular palsies and diplopia, it is important to state that in very few of our cases were actual paralyses of the ocular muscles demonstrated. We were inclined to attribute the diplopia, in the cases observed, to lesions, probably, of the posterior longitudinal bundle. A similar phenomenon has been observed in epidemic encephalitis, where patients would frequently complain of diplopia and yet show no demonstrable ocular palsies.

The disturbances in sensation, involving the posterior columns, were much more definite than those involving the spinothalamic pathways. Birley and Dudgeon have called attention to an acute cervical ataxia, giving rise to the so-called useless arm, described by Oppenheim.

With regard to the recession of signs in multiple sclerosis, we have found in a number of our cases even paraplegias to disappear, but to recur after intervals varying from months to years. It has also been noted that even in the well-established cases from time to time additional clinical evidences of disease appear. This has its basis in modern pathological studies which show, beside the old lesions, new foci as evidence of the extension of the process to new areas.

Dr. Strauss: When Dr. Sachs, under compulsion, tried to give a pathognomonic symptom group, I wondered if he would not include in that symptom group this fact: That we are often impressed by the possibility of multiple sclerosis in a case in which the symptoms are so diverse that they cannot be grouped under any one systemic disease, and the very diversity of the symptoms makes one always suspicious of the possibility of a disease such as disseminated sclerosis.

Secondly, I notice on this chart there is no mention of a symptom which is recorded as not common, but very important in multiple sclerosis. There are cases in literature, as some of us

probably have observed, of individuals who are blind for a short time and in whom at that time the ophthalmoscopic picture shows no change in the disc.

Dr. Sachs: I think it is perfectly true, as Dr. Strauss intimated in his question, that whenever there are widespread symptoms, or symptoms pointing to multiple widespread foci, there are only two or three different conditions that can be at all considered. I have been in the habit of saying that if the disease points to multiple foci, we can think only of multiple sclerosis, of multiple syphilis, of general tuberculosis, and, of course, of multiple tumors of some other sort; those are the only processes that give rise to multiple widespread foci. So that it is natural, I think, to suspect disseminated sclerosis, or at least to consider it, when the symptoms are widespread and diverse.

Dr. Strauss is also correct, I think, in saying that there are some cases in which transitory blindness may be an initial or an early symptom of disseminated sclerosis. It so happened that we have had no case of that sort. It is mentioned in the literature. I have no doubt there are some other symptoms that have been omitted here, that may occasionally occur in a case of disseminated sclerosis, but on the whole I think the grouping as we have arranged it there covers a sufficient number of reliable symptoms and symptoms occurring often enough to necessitate their consideration in establishing a diagnosis.

Dr. Hunt: I would like to ask if you regard the presence or absence of fever and reactive changes in the blood-stream as of any importance in the symptomatology of multiple sclerosis, which is probably an inflammatory affection of the central nervous system?

Dr. Sachs: Of course, I could not include it as a factor in the disease, once the diagnosis is well established, but that it may play a part in the earliest stages of the disease I must concede. However, I do not know that any of us, given a patient who has symptoms that are at all suspicious of disseminated sclerosis and allowing for a febrile movement, would be helped by that febrile movement to establish the diagnosis. On the contrary, I think we would all be a little bit timid about the diagnosis if there were that febrile movement present. But I should be very much interested if anyone could claim that he observed even the initial fever. However, if you meant febrile movement in the course of the disease, I would say my experience has not led me to attach any importance to that in the establishment of the diagnosis.

Dr. Patrick: I would like to ask if Dr. Sachs has seen any case of optic neuritis in multiple sclerosis?

Dr. Sachs: So far as our records go, I do not know whether there is any case. Dr. Friedman nods again; he knows all the particulars better than I do.

The thing that is characteristic of multiple sclerosis is a primary atrophy. According to the records, temporal atrophy was noted in 46 cases; in 11 cases there was blurring of the discs or mild optic neuritis. You see, there again is a symptom that you cannot make use of as a positive symptom of a disseminated sclerosis, and for that reason the presence of an optic neuritis would, to my own thinking, militate against the diagnosis of disseminated sclerosis rather than its support, and for that reason I did not include it in this chart.

On the Significance of the Sequence and Mode of Development of Symptoms as an Aid to the Diagnosis of Multiple Sclerosis in the Early Stages

Williams B. Cadwalader, M.D., and John W. McConnell, M.D.

Multiple sclerosis is regarded by European authors as one of the most frequent conditions that affect the central nervous system. Great stress must be laid upon all the points in the history, to show the sequence in the development of subjective and objective signs arising during the course in a given case. This view is of great importance in diagnosis, since it brings about a broader conception of the disease and tends to create a unanimity of opinion, as well as to help toward an appreciation of the mildest types of the disease that might lead to the realization that abortive cases or spontaneous cures do occur.

In the earliest stages of multiple sclerosis many of the symptoms are so mild as to escape detection. It must be remembered, however, that these symptoms may subside without leaving any trace, and yet recur later and become progressively more intense.

If, in a given case, spastic paraplegia, intention tremor, scanning speech, optic atrophy, and nystagmus are present, the diagnosis presents but little difficulty, since these symptoms point to an advanced stage of the disease. But in the earliest stages of multiple sclerosis, before any of these signs

have developed fully, the diagnosis is exceedingly difficult. The point that we wish to emphasize and discuss at this time is that a knowledge of the mode of succession of the symptoms may constitute sufficient evidence on which to base a positive diagnosis in the early and undeveloped stages. Isolated objective signs, such as impairment of vision, ocular paralyses, weakness of one or more of the extremities, associated with paresthesia are exceedingly common. These phenomena are, however, transitory and are frequently so fleeting as to be overlooked.

Remission of the onset symtoms is far more common than is generally believed, and is prone to occur in the majority of cases. Birley and Dudgeon (*Brain*, London, 1921 xliv, 150) have shown that most cases run an intermittent course, accompanied by a haphazard series of relatively acute disturbances due to focal lesions.

In one of the cases studied at the University Hospital the earliest evidence of the disease—dating back to 1907—was a paralysis of the left leg that lasted one month, disappeared, and returned within two months. It was absent again for a prolonged period, but in 1909 it recurred, and remained as an intermittent feature up to and for some time after the full development of marked bilateral spastic paraplegia and other symptoms of multiple sclerosis—about eight years later.

This case shows that transitory paralyses may constitute the only objective sign of disease, and may recur and subside at irregular intervals, covering a period of time varying in duration from months to years, gradually becoming fixed and permanent, and later associated with other manifestations characteristic of the late stages of multiple sclerosis.

In one of our cases the only complaint was of intermittent diplopia over a period of three years before other characteristic signs developed. In another case there were irregular attacks of sudden but transient blindness preceding the development of optic atrophy; and in still another case there developed very rapidly bilateral oculomotor paralysis that persisted for eighteen months, no other symptoms, either objective or subjective, being present. Tremor, scanning speech, and weakness of the extremities developed

later. Another case presented the signs typical of hemiplegia of rapid onset, which had been mistaken for the results of an apoplectic attack from vascular occlusion; these persisted for a number of months without the development of other symptoms.

For diagnostic purposes isolated symptoms of the disease under consideration are of little value, but the knowledge that paralytic phenomena were at first isolated and later became permanent and were combined with nystagmus, scanning speech, tremor, or other manifestations, may be of considerable importance.

It has been our experience that the classic symptoms, i.e., nystagmus, scanning speech, and intention tremor, differ from the other signs of this disease in that they are not so frequently remittent in character, although occasionally they appear as isolated signs. Once established, they tend to become permanent and to progress. Each of these symptoms seems to point to a more or less widespread distribution of the inflammatory lesions, and for this reason they are of far greater importance than almost any other single sign of the disease. Scanning speech or other dysarthria indicates disturbance in the combined motor function of the respiratory, laryngeal, palatal, lingual, and lip muscles that are supplied by different cranial nerves; and each one of these cranial nerves has its origin at a different level within the brain stem. One lesion sufficiently severe to have destroyed all of these must, therefore, be very diffuse.

A purely spinal type of multiple sclerosis is exceedingly uncommon. It is not unusual, however, to find that a diagnosis of multiple sclerosis has been made when the symptoms of spastic paraplegia and loss of abdominal reflexes are present without any involvement of the structure of the brain. In our opinion this is not always justified, although we do not deny that the disease may present this picture. A case of this kind was reported in 1900 by Burr and McCarthy (*The Journal of Nervous and Mental Diseases*, 1900, ccvii, 634), the diagnosis having been confirmed by autopsy, but which presented only the signs of combined sclerosis of the spinal cord. When, however, these symptoms are followed by nystagmus, intention tremor, or scanning speech, the diag-

nosis is, we believe, clear. Such a case recently came to our notice, in which spastic paraplegia had existed for two years after which nystagmus, scanning speech, and tremor of the upper limbs rapidly developed. Other cases have been reported in which symptoms attributable to the spinal cord were entirely lacking. Here, again, in the absence of the classic trio—scanning speech, nystagmus, and intention tremor—the diagnosis may be uncertain. Thus in one case bilateral oculomotor paralysis developed very rapidly in the spring of 1919, and persisted for eighteen months, although no cause for it could be found. Months later, however, the patient began to complain of difficulty in writing with his right hand, due to tremulousness. This tremor gradually extended until now it involves the four extremities, and is associated with moderate weakness in the right lower limb, increased tendon reflexes, and the Babinski sign, ankle clonus, and scanning speech. At the beginning a diagnosis of multiple sclerosis was impossible, but now that the other symptoms have developed, together with the involvement of the lower limbs, the diagnosis seems quite clear.

In conclusion, we would emphasize that the sequence, mode of development, and the combination of signs are more important than the individual symptoms themselves. In addition, the occurrence of cerebral symptoms, most particularly scanning speech and nystagmus, either alone or after spinal symptoms have developed, or the reverse, spinal symptoms following the cerebral manifestations, is strongly indicative of the dissemination of the pathologic process. If there is a history of earlier remissions or of a discontinuance of the process in the early stages, followed by a progressive course, the nature of the disease can be determined with confidence.

Cases

Case I. J.K., Aged eighteen years.

Chief Complaint. Tremulousness.

Family History. Negative.

Personal History. Was well until October, 1918, when he was very ill with "Flu." Was confined to bed for two weeks; fever and delirium were present and patient was extremely weak. He gradu-

ally recovered from his acute symptoms, and was out of bed in about four weeks. Although believed to have fully recovered, he states that he has never regained his strength, particularly in his lower limbs. About January, 1919, while driving a motor car at night and looking at the headlights of another car approaching, he first noticed diplopia. This has been irregular and inconstant, but most annoying. During this time he has developed very gradually, weakness of the lower limbs associated with marked tremor and uncertainty in gait. General health remained fairly good.

Examination showed weakness of the right sixth and of the left third nerve; marked intention tremor of all four limbs; adiadokokinesia on each side; dysmetria in both upper limbs; marked ataxia and spasticity of both lower extremities; increase of all the tendon reflexes; ankle clonus on the right, and Babinski sign present; speech is slurring.

Diagnosis. Multiple sclerosis developing after an attack of "Flu."

Case No. II. E.Z.D., white, male, aged thirty-three years. First examined April 20, 1911.

Chief Complaint. Weakness of the left leg.

Family History. Negative.

Personal History. The patient is a highly educated man. He has been partially blind since 1908, the impairment being due to unilateral optic atrophy, considered by the ophthalmologist to be the result of a sphenoidal sinusitis. There was some difficulty in convergence at this time, believed to have been due to weakness of the internal rectus muscle of the left eye. About a year preceding the difficulty with his eye (1907) he noticed a weakness of the left leg which lasted about one month, disappeared for two months, then recurred for about a month, disappeared again, and recurred in 1909. Shortly after the last recurrence he experienced difficulty in writing and in shaving, which he attributed to weakness and stiffness of the right hand and arm.

Following the appearance of these symptoms he gradually developed a spastic paraplegia, scanning speech, and intention tremor—a typical picture of *disseminated sclerosis*, from which condition he is suffering at the present time.

Blood Wassermann negative.

Case III. K.N., white, female, aged eighteen years. First examined in 1905.

Chief Complaint. Nervousness.

Personal History. For about a year she has had attacks of double vision lasting for varying periods of time, the longest being seven weeks. After several attacks of double vision during a period of

three years she gradually developed a marked tremulousness of the hands and noticeable disturbances of speech. Following this her symptoms progressed quite rapidly, and she died two years after first coming under observation. This was a typical advanced case of *disseminated sclerosis.*

Case IV. W. W. P., white, male, aged twenty-four years. First examined February 2, 1916.

Chief Complaint. Nervousness.

Personal History. The patient states that he was perfectly well up to December, 1915, at which time he suffered a severe nervous shock, and immediately after noticed that his vision was blurred. Within a few days he became blind and had some trembling of the hands and a slight difficulty in walking. All these symptoms disappeared completely. About two weeks previous to his admission to the hospital he again developed tremulousness of the hands, and had considerable difficulty in using his legs for locomotion. He gave no history of excesses of any kind, and was a man of unusual education and of splendid physique.

Physical examination at the time of his admission to the hospital presented the neurologic features of a fairly well-advanced case of *disseminated sclerosis,* namely, intention tremor, scanning speech, spastic paraplegia, and optic atrophy.

He remained in the hospital for a short time, and was under observation for about two years. Within six months after leaving the hospital he improved so greatly that he was regarded as almost completely recovered. This remission in the symptomatology was of very short duration, however, and the symptoms that followed progressed with tremendous rapidity. At this time he presents a picture of a well-marked case of *disseminated sclerosis,* and is almost helpless.

Wassermann reaction, both of the blood and of the spinal fluid, was negative.

Case V. J. W., aged seventeen years.

Chief Complaint. Headache and inability to look upward.

Personal History. In May, 1919, following an acute attack that was diagnosed as "Flu," and that had confined him to bed for two weeks, the patient found that he was unable to look upward or downward, and had frequent severe frontal headaches. On examination in June, 1919, there was inability to rotate either eyeball upward or downward, although the external and internal rotations were performed normally. No cause for the condition could be determined, and no other objective sign could be discovered. The patient continued under observation at the Presbyterian Hospital, and about October, 1919, he complained of an

inability to write because of tremor of the right hand. This condition progressed, and weakness of the right lower limb also developed. About 1920 his speech became indistinct, and in 1921 examination showed partial bilateral third nerve paralysis, with marked scanning speech, intention tremor, dysmetria, and adiadokokinesia on both sides, but most marked on the right, weakness of the right lower limb, with ankle clonus and increased tendon reflexes.

Diagnosis. Multiple sclerosis.

Case VI. M. S., white, male. First examined at the Philadelphia General Hospital.

Personal History. Patient was almost completely blind. The right half of his body was practically powerless, and he had considerable difficulty in using the left side of his body. Nevertheless, he was able to move about. The history of his present illness was to the effect that about a year before coming to the hospital he had a sudden attack of what was believed to have been "an apoplectic stroke, which resulted in paralysis of the right arm and right leg." This was soon followed by failure of vision, which gradually grew worse.

On admission to the hospital he presented weakness of all four limbs, but greater on the right side; a partial blindness, due to optic atrophy; slurring speech; marked nystagmus; tremor of the left upper extremity following use of the limb, marked increase of all the reflexes, and bilateral Babinski sign.

Wassermann, both of the blood and of the spinal fluid, was negative, as was also the general physical examination.

Diagnosis. Disseminated sclerosis. The disease pursued a continued progressive and typical course up to the time of death, which occurred in 1921.

The following questions submitted to Dr. Cadwalader before the Commission, together with the answers to them, are here reported verbatim.

Dr. Hunt: It has been stated that the course and sequence of the symptoms, rather than individual symptoms, are more or less characteristic of the symptomatology of the disease. Would you say that you could distinguish a multiple sclerosis from what we might say is another form of inflammatory affection of the central nervous system of a non-suppurative nature? In other words, is there anything in the symptomatology of multiple sclerosis which characterizes it as a special disease entity; as being different

from any non-suppurative multiple inflammatory affection of the central nervous system; of perhaps variable etiology?

Dr. Cadwalader: I think I can grasp what Dr. Hunt has in mind, and in answer to his question, I would put it this way: Our own conception of multiple sclerosis is that it is an inflammatory disease of the nervous system. We do not know what the cause of that inflammation is. We do believe, and there is considerable evidence to show, that there is more than one cause that can give rise to that inflammation and that those different causes produced the same kind of inflammation as seen under the microscope, presenting exactly the same picture in many instances (not in all instances by any means). The point that Dr. McConnell and I wished to emphasize was that in any given case where the history is complete and adequate, the knowledge of the onset of given symptoms and their sequence of development and intensity up to the time the patient is examined, together with the remissions and the period of absence of symptoms, finally ending in an increase of those same symptoms in association with additional symptoms into the classical picture with tremor, nystagmus, scanning speech and other forms of motor paralyses, is the important thing.

I would emphasize the fact that my own personal feeling is that during the last two or three years I believe I have seen more cases of multiple sclerosis than formerly. Now it may be it is because I was thinking of this meeting; but I really believe that there are many cases, as Dr. Sachs has mentioned, that are perfectly definite, clinically, so far as clinical signs are concerned, definite cases of multiple sclerosis, with all the classical symptoms. Their mode of onset is a little bit different in my experience (I am speaking of the 14 cases which I had), because in each one they were preceded by an attack regarded as "Flu." A few weeks or a few months following, the patient developed the ordinary picture of a mild type of epidemic encephalitis, then these paralyses developed, and after about six months' time they presented the typical classical picture of multiple sclerosis.

But there is one point that I feel is important enough to mention, although I do not feel certain of it, and that is that in those cases that I have seen, there is a tendency to progress right straight along, without intermission, without remission, and one of these cases now is bedridden. It is about a year and a half since the onset.

Now, I would attribute that to a previous attack of epidemic encephalitis. On the other hand, in the cases of post-epidemic paralyses or epidemic encephalitis, the residual paralysis such as the Parkinson's type of disease that we know so well, I have never

seen progress after having once become fully developed; that is to say, the cases that we have observed, that developed the Parkinson's type of disease, go on progressively up to a certain point, say, ten months—I am not sure that that is perhaps correct, but less than a year; then they remain stationary and they do not progress from that time on, at least we have not seen it; but the multiple sclerosis types of epidemic encephalitis have progressed and become bedridden. That is an observation; I do not know whether it is too soon perhaps to make these conclusions.

Dr. Hunt: I would just like to reenforce my previous question. Your conclusion then is, from the symptomatology, we should regard the symptomatology of multiple sclerosis as we do that of meningitis, as simply a symptom complex, which in the present state of our knowledge does not enable us to distinguish one form of multiple inflammatory involvement of the central nervous system from another form; that there is nothing in the symptomatology of what we call multiple sclerosis which is characteristic, which serves to separate it from other multiple inflammatory infections of the central nervous system.

Dr. Cadwalader: No, Dr. Hunt, I did not mean to say that. I do believe, and Dr. McConnell also believes, that multiple sclerosis is a real separate entity, that it is a disease with special symptomatology. I wish to say that I do believe that there are other infections which may cause lesions that may produce symptoms which will give great difficulty in diagnosis by ordinary clinical means, but that these are rare and uncommon. I would put it that way. Does that answer your question?

Dr. Hunt: Well, what would be the distinguishing features?

Dr. Cadwalader: I do not know any.

Dr. Hunt: Then there are none in the present state of our knowledge.

Dr. Cadwalader: I would say there are certain cases that we cannot separate from other conditions, but I do think that multiple sclerosis is a separate and distinct disease.

Section II

The Mental Manifestations and the Emotional and Psychological Factors in Multiple Sclerosis

The mental manifestations of multiple sclerosis are presented by Drs. Sanger Brown and Thomas K. Davis of New York City.

The emotional and psychological factors bearing upon the development of multiple sclerosis are discussed by Dr. Smith Ely Jelliffe of New York City.

The Mental Symptoms of Multiple Sclerosis

Sanger Brown, 2nd, M. D., and Thomas K. Davis, M. D.

Despite the descriptions of mental symptoms in multiple sclerosis which are found in the literature, it is difficult to get in this way a comprehensive idea of their character. This is because the mental symptoms are of several patterns and writers vary in regard to what symptom they stress. A cursory view of the subject shows that there is not in multiple sclerosis a group of symptoms as consistent as the fairly consistent symptoms seen, for example, in general paresis. However, counting the euphoria, probably in 90 per cent of cases there are mental alterations which warrant the meaning commonly granted to the term "mental symptoms." It is because they are overshadowed by physical symptoms and so often are of a character to introduce no element of alarm that frequently they are disregarded. Generally speaking, the multiple sclerotic patient cannot carry out the things which might lead to committment. This factor makes it not surprising to find that there were only 3 cases of multiple sclerosis among the 6,700 insane patients in the Manhattan State Hospital.

We have not been able to demonstrate any predisposition to mental disease in the make-up of these patients. In other words, the mental symptoms seem more dependent upon the organic brain disease than upon an underlying tendency.

Keeping in mind a few illustrative cases and referring to them briefly, we will take up different symptoms independently.

Euphoria. Many patients with multiple sclerosis have a slight elevation of mood which may be termed euphoria. Although suffering from a serious disease, they do not think of their condition as serious, nor do they seem deeply concerned about it. It consists of a marked inconsistency between the patient's mood and his physical disability.

The following case is an illustration of this mildly euphoric state so often seen.

A woman, thirty-one years of age. She had had symptoms of multiple sclerosis for over ten years, and she has been in the Montefiore Home for three years. From the physical standpoint she is a very advanced case. She cannot walk, she is nearly blind, her speech is so indistinct that she can scarcely make herself understood. She is so incoordinate in movement that she has to be spoon-fed.

Despite the fact that she is reduced to a state of complete helplessness, she is very optimistic and cheerful, laughs and jokes about her symptoms and is not in the least concerned about her condition. Neither is she demented. She can give a full account of her past life without any discrepancies of memory. Euphoria was seen in 10 of the 14 cases showing mental symptoms which we had the opportunity of examining.

The euphoria often becomes much more marked, and the expansive mood of a manic-like state may result. A few cases are described in the literature which showed delusions of grandeur similar to those seen in paresis.

The cause of the various euphoric states in multiple sclerosis is not known. Mood changes of this general character occurring in greater or lesser degree in several organic brain conditions—the euphoria of paresis, the facetiousness often in brain tumor—are also not at all clearly explained.

States of Mental Depression. A number of cases has been reported in the literature where multiple sclerosis cases have developed suicidal ideas, and attempts at suicide have been made.

Mental Deterioration. It might be expected that in a progressive organic brain disease such as multiple sclerosis, marked mental deterioration would occur in all patients. This is not the case. In many instances even where the disease has persisted for years, changes of this character are very slight or amount only to a chronic mental tension defect. On the other hand, it is not difficult to find occasional badly deteriorated cases.

Deterioration, in brief, may or may not occur, though probably it is present in a majority of cases. It progresses

to different degrees in different patients, only occasionally becoming profound; and, as would be expected, as it develops, it obliterates, to a large degree, trends which may have been present.

Some cases show only a mild disturbance of memory, of which they are entirely aware.

If one is to believe the literature a few cases have shown Korsakoff-like pictures. But we have found no such cases and feel that this type of case is very rare.

Hallucinations. Auditory hallucinations without insight and occurring as a feature of a delusional trend are not unusual.

We have to report a single example of considerably more bizarre hallucinatory phenomena. In one case observed at the Neurological Institute there were visual and auditory hallucinations with quite clear insight.

The patient is a woman, thirty-one years of age, and her physical symptoms have existed for two and a half years. For many months she has had visual hallucinations as follows: The rug appears to be on fire, and smoke issues from the carpet. She has seemed to see bright green beetles crawling on the window-pane. Occasionally she has seen people approach the door, and has not known definitely until reassured, that no one was there. The quite remarkable feature is that she has perfect insight into these experiences. She cannot be said to be suffering from a psychosis and she realizes that these false impressions are caused by her disease.

On one or two occasions she has had hallucinations of hearing, such as a band playing, or voices singing. There are no hallucinations of taste, touch or smell. Examination of the eyes shows 20/50 vision in the right eye; 20/70 in the left eye; with temporal pallor of the optic discs, and some contraction of the visual fields.

The nature of these hallucinations suggest that they arise on some irritative or toxic basis, either in the higher visual centers or in the pathways leading to them.

Trends. Cases are seen which bear a certain resemblance to dementia præcox of which the following is an example: This woman is thirty-three years of age. Her severe mental symptoms started after the disease had existed for nine

years. Although she was entirely blind at that time, she thought people were watching her, came into her room at night, and were threatening to kill her. She spoke of hearing voices then. Much of her thought content had to do with sex affairs. She thought that men were paying her attention with the idea of marriage.

Although bedridden and entirely helpless she still talks about the possibility of marriage. However, these paranoid trends have almost entirely disappeared and now she is mildly euphoric, or at least contented and happy.

In this case the delusional trend and hallucinations may be less directly dependent upon an organic lesion and appear to be more of a dementia præcox-like nature. In none of our cases have we found negativistic phenomena or catatonic reactions.

Personality. Apart from certain mood changes, for example euphoria, multiple sclerosis patients usually retain the same personality that they had before their illness began.

The multiple sclerotic patient, even though deteriorated, does not as a rule show marked moral and ethical changes, and there is comparatively little of the grave disturbance of personality common to paresis.

Course of Mental Symptoms. An interesting characteristic of the mental symptoms in multiple sclerosis is their marked tendency toward change and progression. Very often the paranoid trends and delusional states are of but a few months duration. The brevity of their stay may be quite unexplained. Or again they may disappear as the deteriorating factors advance. With the subsidence of trends, there is a tendency for the euphoria to assume greater intensity and grandiose elaboration of the euphoria may be a very late development.

Conclusions. From our observations we would divide the mental symptom of multiple sclerosis into two groups: First, those which are primary and directly the result of the organic lesions; second, those which are incidental and secondary.

In the first group we would place euphoria, since it seems to be associated with the organic brain condition; likewise, the mental defect symptoms, the occasional hallucinations of organic origin, and the very rare confused states and the

Korsakoff clinical pictures. We would also place here the occasional terminal states with delusions of grandeur.

In the secondary group of symptoms we would place those transitory delusional states and depressions which appear to arise as a result of the handicapped and incapacitated condition in which the patient finds himself.

Here may be suicidal attempts, delusional trends accompanied by hallucinations often of only a few months' duration. There are still other delusional trends which are more like dementia præcox. However, marked distortion of thought and oddities of conduct which are so frequent in dementia præcox are not met with in multiple sclerosis.

While multiple sclerosis has symptoms in common with other organic brain diseases, the mental symptoms do not resemble these conditions very closely. The clinical picture is not like that which is seen in paresis. It is not like that of cerebral arteriosclerosis. The symptoms are more similar to those occasionally seen in brain tumors.

It is reasonable to suppose that the secondary symptoms such as depressed states, and the paranoid symptoms, depend to a considerable extent upon the mental make-up of the patient before the disease developed; but with the primary symptoms of the disease this is not the case.

The following questions submitted to Dr. Brown before the Commission, together with the answers to them, are here reported verbatim.

Dr. Campbell: I should like to ask one or two questions, perhaps merely to clarify that to which Dr. Brown has already called attention. Dr. Brown separates the cases with mental symptoms into two groups, one of which shows symptoms which are the result of the organic lesion, while in the other case, the symptoms are looked upon as secondary. I did not quite grasp why the euphoria should be looked upon as organic, while the depression should be looked upon as secondary. Perhaps Dr. Brown might tell us whether that is on the basis of euphoria in other organic conditions, such as general paralysis.

I wondered whether Dr. Brown had, in his series, careful intelligence tests made and whether he found this uniform impairment of intelligence.

I should also like to ask Dr. Brown whether, in those cases presenting psychotic pictures somewhat like a mania or a depression or a schizophrenic condition, paranoiac or otherwise, the similarity was somewhat superficial; or whether, on the other hand, there was reason to think that the organic condition was a real factor in the schizophrenic degeneration, just as we might have a schizophrenic degeneration coming on after childbirth or some toxic condition?

Dr. Brown suggested the possible relationship of the mental symptoms to the personality of the patients. I should like to know whether he was able to trace that out in detail in his cases?

Dr. Brown: In respect to the placing of euphoria as an expression of the organic nature of the disease, I had placed that there because one does see it in paresis and I think one frequently sees it to a mild extent in organic brain diseases of various kinds. Sometimes one sees a very mild type of euphoria in arteriosclerosis and it was for that reason that I considered it organic.

As to the impaired intelligence occurring in all cases, I could not demonstrate any impaired intelligence in the few cases that I saw. I could not demonstrate impaired intelligence, or judgment, or memory. However, even with those cases, I think one would have to say there was some mental change because there was in them the slight tendency to be a little euphoric — a little changeable in mood perhaps, so that I felt even in those cases, while you could not say they had a psychosis by any means, they were not normal mentally, or perhaps not quite what they were before this condition began.

As to the resemblance of this to a monomaniac state or a dementia præcox, I felt that was superficial. The monomaniac condition changed. The dementia præcox-like trends in the very few instances that we saw, were also not enduring, and so for that reason, I thought the trends at least were the situation type of psychosis, the patient finding himself in an incapacitated condition.

As to the type of personality which develops the psychosis in multiple sclerosis, I would say that we were rather surprised to find that in nearly half of our cases, it looked as if they had been rather unstable from a mental standpoint before the development of the organic disease, but I hesitated to draw deductions from that. That the previous personality had played an extremely important rôle, in view of the serious organic brain disease, would seem probably to be the most important thing.

Dr. Taylor: Dr. Brown, would you make any definite attempt at correlation or localization? Would you consider, for example,

that euphoric conditions were due to plaques of sclerosis in the frontal lobe, or other symptoms—hallucinatory and others?

Dr. Brown: I have felt that in regard to the mental symptoms one could not make any correlation which would be warranted between symptoms and lesions.

Dr. Hunt: I would like to ask if you have any statistics as to the number of cases of multiple sclerosis, that might be insane and treated at institutions for the insane?

Dr. Brown: I was unable to get that, Dr. Hunt. In the New York State Hospital service there are, apparently, in all the state, I do not think over a dozen cases, and perhaps this is overestimating the number.

Emotional and Psychological Factors In Multiple Sclerosis

Smith Ely Jelliffe, M. D.

In this discussion Dr. Jelliffe develops two issues. I. He first considers the prevalence of neurotic and psychotic disturbances in patients who show the usual somatic sensorimotor disturbances of what is usually termed multiple sclerosis, irrespective of the etiological factors. In this section of the discussion of the emotional and psychological factors, multiple sclerosis is but a general convenient label for a whole group of syndromes which more closely conform clinically to a pure abstraction, the diagnosis, "Multiple Sclerosis."

Such neurotic and psychotic disturbances, in this section, viewed from the psychological aspect are dealt with from two points of view. (*a*) Those which are due so far as analyzable to problems connected with the location of plaques in different parts of the nervous system, independent of the pathological nature of the plaques, the psychological symptoms are discussed purely from the standpoint of the localization of the offending focal lesions. Localizations of plaques within the zones of language produce characteristic aphasic problems of a vast variety too detailed to be entered into. Those of the frontal lobes produce some very characteristic mental pictures. Memory losses, *witzelsucht*, confusions, etc. Similarly, midbrain involvements cause a variety of emotional dyskinesias as seen in the explosive

laughter, crying, etc. Other strictly localizable disturbances of gestures, mimesis, or other type of symbolic expression, from lowest to highest stages of expression are discussed briefly.

Dr. Jelliffe then considers a second type (*b*) of psychological reaction which by insensible degrees is correlated with the second main topic of his theme. In one sense it is separated only with difficulty from it. What are the compensating psychological manifestations which the patient builds up in the face of disease, which according to the intellectual or intuitive grade of development of the patient is recognized, sooner or later, as chronic, progressive, disabling and may be fatal? What are the psychological attitudes which grow up in a vast kaleidoscopic mosaic-like series of reactions made possible as compensations for ills, or well defined disturbances of more or less important functions?

One sees types of hallucinatory prowess in the sexual sphere in patients who have had plaques preventing the penis erection, or vice versa, some interesting observations of ideas of sinfulness in compensation for persistent priapism from cervicodorsal localizations of plaques. Plaques cutting off bladder automatisms are responded to frequently with great irritability and restlessness and fussiness. Some women patients with periodic bladder disturbances drive their environment to distraction in their constant exasperation connected with impaired bladder function.

Muscle power loss may be reacted to in a great regression to psychological helplessness. These patients may always demand amusement. They look for new friends in every face. They live on being mothered or fathered. They must have comfort, if wealthy; and when poor, despair may be the reaction. A light, debonnair air of cheerfulness is frequent in many. They whistle, as it were to keep their courage up. Or again alcohol and drugs are the means taken to exclude reality. Alcohol seems greatly shunned, however, as it works such speedy loss of power, long before its psychological blessings are conferred. This is an interesting problem of a pharmacological and pathological correlation.

In an ingenious manner, Brouwer has shown how in some types of multiple sclerosis the newest accessions of neurologi-

cal function fall down before the pathological process much earlier than the phylogenetically older functions. This also is known to be a general law in the pharmacological action of alcohol; thus by a process of summation of similars, a much greater functional loss is found following even the most minute alcohol dosage. Nevertheless the flight into alcohol sometimes is quite a marked symptom. Its underlying relations to a progressively arrived at suicide is of far reaching psychological importance.

Other types of psychological adjustments to specific losses are instanced in the paper.

II. Under the second theme Jelliffe passes to an entirely new series of considerations. He goes over from a discussion of psychological situations as results of the variety of pathological factors which clinically result in a multiple sclerosis picture to entirely new points of view.

These must be very sharply differentiated from the others. He now asks a question whether psychological factors may not be conceived of as the *cause*, not of "multiple sclerosis," as some ignorant or malicious critics have implied, but as playing an important if not determining rôle in some special types of multiple sclerosis. From the foregoing discussion it is revealed that he first regards our clinical concept of multiple sclerosis as a syndromy. It has steadily achieved greater and greater precision; and analytic research from the days of Vulpian, Charcot, Gilles de la Tourette, Valentiner and the workers between 1852 and the present time is showing what a multiplicity of factors are playing a dance of variable importance, as we attempt a synthesis of this or another trend. Thus the syphilitic encephalomyelopathies causing a multiple sclerosis picture were easily eliminated. The last epidemic of encephalitis has left in its wake a comparatively large group of very interesting multiple sclerosis by-products. Between may be found in varying degrees of pathological sharpness and etiological significance other cases of multiple sclerosis. There still remains and has remained all throughout this gradual analytic-synthetic process a tendency to rally around the concept of an *essential or primary sclerosis*, a type of intellectural acrobatics which is also seen in the considerations attendant upon the many

problems found in that enormous diagnostic scrap-basket, epilepsy. Here at least a thousand etiological and pathological conglomerates have been found and yet a residue of essential epilepsy is clung to by many.

It is to such a concept that the author directs his attention at this time. It is within this group, the causes for some of which no tenable hypotheses have been formulated, that he would suggest further search, and this time into psychology. In certain of these types vascular lesions stand in the foreground. These seem to be in the nature not of inflammatory reactions, but some vessel wall disturbance of the nature of or related to analogous vascular phenomena, which have been studied as oedemas, etc. The "exudative diathesis" is the concept which has attempted to correlate these phenomena. In the selected *few or many* cases—no one yet is in a position to say how many or how few—Jelliffe considers the vascular regulating mechanisms in the neuraxis, in their relation to the functional work they are called upon to do. Thus a foot-ball kicker, or a runner, or a rower, or anyone performing a definite job, imposes upon the integrating activity of the nervous system a definite series of patterns: Certain cortical association bindings; certain pyramidal pathway regions; certain synaptic junction bridges, and certain anterior horn cells, and certain muscle end plate cells, all get together, function more intensely and put over the pattern in purposeful action, for the individual and for the race.

This is the type of all activities, all behavior. Now in all this synthesis the vascular mechanisms, including the lymphatics and veins, are playing a very important rôle. The humoral side, the material, chemical side of the whole action pattern must be attended to; and specifically attended to. Any defect in any of the biochemical ingredients throws the orderly working of the required pattern out of line to a greater or lesser extent. This, for instance, may be seen in the defect in calcium in its relation to muscle jumpiness, as tetany, spasmophilia, tremor, etc., varying quantitatively and coordinatedly with the synaptic junction regulation brought about in part by the calcium content. Neurological regulation of metabolism is a very pertinent fact. The

organism as a whole functions by means of and through the nervous system, and it is the vegetative nervous system, the phyletically primitive nervous system, which is serving chiefly in this synthesis of metabolites and through the vascular mechanism.

Now the author would attempt to link up emotional factors with the orderly working of this whole action pattern synthesis.

Here he leaves the high road of conventional psychology and seeks for emotional disturbances in the unconscious. Every one knows how conscious emotional factors, which usually are operative for a short time only, and, for the very reason they can become conscious, are capable of discharge at comparatively low states of tension, can produce far-reaching changes in the nervous regulators of metabolism. While fully recognizing the value of this mode of approach Jelliffe proposes to search the unconscious in these patients to see if there are any important emotional factors, which because of their inability to be released in ordinary conscious states of motor activity, are held under strong repressions since strong repressions are invariably correlated with increased tensions. It is not conscious terror, with crying, horripilation, dilated pupils, tremor, etc., in which the patient can release nervous function, by sweating, or crying, or diarrhea or flight, that creates the mischief in the machine. It is the unconscious terror for which no release through projicient displacement can be found that creates the breakdown of structure. To one who has studied the unconscious it is obvious why the cravings cannot be satisfied, and equally plain why terror, not known as such, must be intense. These cravings strike at the very foundations of biological and sociological evolution. They would turn back the progress of the patiently won victories of creative evolution. They are antisocial, anticreative. They would destroy society and the individual, hence they have to be held under. Hence they throw specific stresses upon action patterns which would seek their release. These stimuli are operative all the time, not periodically as in Pavloff's animals, in Cannon's cats, in all of the physiological pecks at the problem, but twenty-four hours out of every twenty-

four, seven days out of every week, fifty-two weeks out of every year; the let-up only occurs in the dream life of the individual, waking at times (creative activities) or sleeping.

Now there is an attempt made to illustrate how the specific vascular needs connected with the action pattern under unconscious stress, with high states of tension, cause the exudative phenomena in the blood-vessels of the nervous pathways intimately related to the function under repression. Illustrative material is offered.

Jelliffe argues that the position thus evolved is quite a simple one. Just go to the unconscious and see what one can see. If there is nothing there, well and good. If on demand the grocer has no sugar, why there is no sugar, that's all, but when it comes to the study of the unconscious in about one-half dozen cases of so-called multiple sclerosis, the situation is quite different. There are difficulties which are of great importance from the psychopathological point of view as developed by recent studies of unconscious processes.

He says that as yet the appraisals of the emotional tension factors in relation to findings of the unconscious are formulating. Whereas external methods of measuring the force of emotional factors have been going on for a number of years, study of internal means of registration are only just beginning.

Here the Freudian conception of the Oedipus Complex is of paramount value. Here is a mechanism which shows the evolution of social integration. The race has grown upward by putting a ban upon its regressive tendencies. This is expressed through a formula which may be followed by means of an understanding of what is happening to the Oedipus Complex. At birth, and until two years of age, no individual analysis has yet been carried out, for obvious reasons. From two to six years of age is the usual period of adjustment wherein the phyletic struggle for sex taboo of the regressive object, the mother, the older woman, the sterile woman, is recapitulated in the life of the child. Repression at five to six has resulted in a progressive aspect towards the love object and towards creative activity.

Repression with sublimation has begun. From this point onward one can trace the successive steps of the evolution of the Oedipus Complex, from its old impossible setting to its successively newer and better settings, making for real evolution in the individual and the race. The steps of this evolution are discernable in the unconscious. The percentage values of regression and of advance are there, dimly discernable.

When one cast in his line in this ocean of the unconscious what stage of Oedipean fish did one find in the multiple sclerosis cases? All of the patients thus far examined showed the marked psycho-sexual fixations at very early stages of this conflict. One patient, a very young multiple sclerotic, had hardly emerged from the uterus in his unconscious phantasies. His general life, if written by a novelist, would reveal him still in swaddling clothes, so attached was he to the parental complex. Another showed a close relation between the location of the symptoms and the patterns of his unconscious cravings which were under strong autonomic states of tension. The blood-vessels broke down where the functional units necessary for nervous release were under the greatest strain. Thus an intense conflict of looking away from his cravings became symbolically patterned in a strong rotation of the eyeballs in a certain direction. This was always more or less consciously resisted. The pull of certain muscles under constant strain, first determined a choroiditis, which extended to the retina. Brouwer's study of the phylogenic situation of the eye muscles, Sherrington's study of the proprioceptive innervation factors and the well known aversion, looking away from guilt, symbolically, are referred to and attempts made at their correlation to show how the vascularization of areas under stress may be gravely affected. Jelliffe goes into specific details of unconscious mechanisms and suggests in a purely tentative manner possibilities of correlation here.

He thus comes to a general conclusion that inasmuch as emotional factors are known to produce somatic alterations; that unconscious emotional factors are known to be under greater tension than conscious ones, and are operative more constantly, sometimes continuously during the waking life,

to hold back antisocial cravings, such unconscious emotional factors are capable of producing graver and more lasting somatic alterations. They can produce what we call acute or chronic physical disease. Just what type of disease is caused will depend upon a host of factors, but of these, any particular stress put upon any particular action pattern will determine the direction of development of the organic disease.

A study of the unconscious factors in organic disease therefore becomes of paramount importance. Such attempts have been made now by the author for the past ten years. Other students have come to quite similar results. He gives the literature. This particular tentative sketch of multiple sclerosis is but one of these studies.

He would advocate a study of the unconscious factors, in this disease, because he believes there will be found, in certain types of the disease, certain vascular alterations, which produce the plaques. These plaques interrupt pathways, which cause the visible signs, which at this age of our misinformation in medicine are but a grotesque physical caricature of that which we now label "multiple sclerosis." These vascular alterations occur at certain places where visceral-nerve-arc tensions are paramount. These nerve-arc tensions are dependent upon action patterns held under terrific repression. Since the contemplated actions are repugnant to the individual and destructive to him and to society, they must remain unconscious for a number of reasons well appreciated by students of modern psychopathology.

Jelliffe considers alternative methods taken by patients with similar repressed material. He relates efforts at release of such severe repressions to catatonia, to catatonic brain edema, where it fails, and to certain crippling psychoneuroses —notably compulsion neuroses, and suggests a number of correlated points showing how energy is switched in this or that channel—causing different symptom pictures, all fundamentally trying to handle the same kind of unconscious material. He also would suggest the idea that strong religious and mystic symbolizations are handling similar cravings at more socially permitted levels.

The following questions submitted to Dr. Jelliffe before the Commission, together with the answers to them, are here reported verbatim.

Dr. Campbell: I should like to ask Dr. Jelliffe whether the lesions shown us this morning, in their very peculiar distribution, are at all analogous to vascular areas, and whether the distribution of these lesions could be brought into more specific relationship to the factors which Dr. Jelliffe has emphasized? Or, if, on the other hand, one assumes that it is not so much a question of vascular areas as a diffusible toxin, whether Dr. Jelliffe could deduce the physiological elements, whether conscious or unconscious, producing the distribution of those types shown in the pictures this morning?

Dr. Jelliffe: I think that can very readily be answered. No, it would be impossible. That is something that has been going on for twenty or thirty years and all the various complicating things that might have taken place might, in a very rough manner, be analyzed in the following way: Suppose at this instant two masked men appeared at that door and said, "Hands up," and they had pistols in their hands. Well and good, every man here would get into a projicient motor attitude; the proprioceptors, in other words, of the body would put everybody here into a certain receptive attitude towards that stimulus. It would vary with every individual, naturally, in the place.

If, within a few seconds, I should say (now utilizing a symbol): "Gentlemen, those are two crazy patients of mine. Never mind, it is just a joke," a certain amount of relaxation would take place in all of the various projicient mechanisms that everybody reacted to, causing you to think nothing would happen.

If, however, I did not recognize them then certain things would commence to happen; somebody would dodge under a table, somebody would throw a chair, in fifteen minutes there would be pandemonium, shots would be fired, fire would take place, and it might take a week to clean up the whole general mechanism which started very simply in the course of half an hour—could I, Dr. Campbell, in terms of broken chairs and fire and everything else, explain that initial stimulus? That is what you are asking me. After thirty years of all kinds of conceivable and inconceivable types of reaction and infection and reinfection and all sorts of things, can it be traced back to original emotional factors? No, it cannot. That is not the question I am trying to put before you at all. I am trying to assume that we start at the very beginning of a

possible limited kind of process. In a limited number of these cases it is possible to deposit certain initial emotional factors there, due to the faulty integration of the individual, that can be found by a study of the unconscious. The real relevance of any question, it seems to me, would apply itself to what experience have the gentlemen had in searching the unconscious of these patients and what did they show.

Dr. Hunt: I would like to ask Dr. Jelliffe if this is a principle that he would apply to all organic diseases?

Dr. Jelliffe: I would say that that is a principle which might be conceived as not relevant to all organic diseases, by any manner of means, but to certain types of chronic progressive organic diseases for which the relationship between cause and effect is not perfectly clear.

Dr. Hunt: I would like to ask why he would exclude any one organic disease, if the principle is correct?

Dr. Jelliffe: That would be very simple. An individual with an acute infection such as an anterior poliomyelitis with destruction of a large number of cells, presents atrophies, progressive dystrophies, and so forth. I do not say that the principle would be applicable to conditions of all kinds.

Dr. Hunt: Just to continue, might I ask what group or groups of organic diseases would embody this principle which you are laying down?

Dr. Jelliffe: I am only outlining from personal experience. I can tell you what I have done with certain groups of organic diseases; hence, I can answer your question only to a limited extent.

I think some cases of chronic diabetes are distinctly related to the types of conflicts of which I speak; I think that certain types of chronic arthritis can be analyzed in precisely the same way, and there are a large number of others. There are certain very interesting postural relationships which grow up in response to unconscious conflicts, which posture relationships throw certain strains upon different parts of the body, giving rise to various types of chronic maladjustment leading to chronic disease.

Dr. Sachs: Could you not have written exactly the same thing if we had been discussing tabes dorsalis?

Dr. Jelliffe: No, if we were discussing tabes dorsalis, I might say this, Dr. Sachs, with reference to the problem which I have tried to outline: You know perfectly well that in tabes dorsalis you have such things as laryngeal crises, rectal crises, etc. Let us ask, as regards the cases of tabes dorsalis, why a man has a rectal crisis, rather than a laryngeal crisis? Then I ask why has he the localization of the process in that particular group of reflex arcs?

It may be possible (I put it tentatively), if we are asking the question, "Why is the localization of the process there" (we know all about syphilis), to ask also, "Why was it not somewhere else?" Are there any particular factors in the individual which determine the localization? That is again a question about which I can give some information, because I have studied a few rectal crises, for instance, from the standpoint of the unconscious, and which I can specifically answer in a certain way; that is to say, being interested always in asking the question "why" and never being satisfied with simply the "how," one keeps going deeper and deeper to see why there is a ready infectability, why a certain group is involved.

Dr. Barker: I think Dr. Jelliffe is trying to make us think of the organism as a whole, the person as a whole: His psychic manifestations as well as his somatic phenomena.

I would like to have him give us his impressions of this: Each individual starts with a fertilized egg-cell which has in it the possibilities of development, and the realized person that develops out of that egg-cell depends partly upon the composition of that fertilized egg-cell, partly upon the environmental influences, internal and external, which react upon it before and afterward; so that what I am today is largely the resultant of those two forces.

I gathered from what Dr. Jelliffe said that he thought both factors were concerned. What starts in the egg-cell is what Kraus calls the genotype—the realized person at any given moment in development is the genotype. Is it your impression that the predisposition to multiple sclerosis, to be definite, depends more upon that genotype or the fertilized egg-cell's limitations in the first place, or upon the reactions that have occurred, or upon the environment of that fertilized egg-cell afterwards; in other words, upon infections, intoxications, and so forth? Have you been able to formulate in your mind whether both are concerned or one is predominately concerned?

Dr. Jelliffe: I am very glad, indeed, that Dr. Barker was nice enough to help me out in saying that these were impressions, because I only wished to convey the idea that they are solely impressions.

I can answer Dr. Barker, it seems to me, in two ways, if I may be permitted. So far as constitutional background is concerned, I have not the slightest doubt that that plays a very large rôle. One factor which has not been brought out in the discussion, so far as I have heard, except in the 3 cases Dr. Brown mentioned—in the 3 cases having multiple sclerosis in one family—is this, that

in the literature there are at least thirty citations of familial multiple sclerosis. These cannot be neglected. But the genotic factor (the constitutional anlage, the constitutional background) undoubtedly plays some rôle in the situation.

Suppose one comes into the world with only three fingers, the genotype, as it were, has reduced you, your constitutional background is below par, you only have three fingers, or you have an inadequate adrenal system or an inadequate thyroid system. What are you going to do with what you get, because you have to meet life as it is, with what you have?

It seems to me that is where the study of the unconscious gives us an extremely interesting episode as to the situation, because the unconscious does two things, or rather tells us two things: It tells us, firstly, something about that constitutional background of which we have sometimes no indication whatever. Secondly, it tells, it seems to me, what type of reactions the individual is endeavoring to formulate to meet that constitutionally inferior background.

Dr. Sachs: How does this fit into your scheme? Many years ago Ettinger, for instance, tried to explain the bladder symptoms of tabes dorsalis from the fact that he traced the history of the patient back to the fact that the person who develops symptoms of tabes has overstrained the content of his bladder, has allowed it to become distended. How does that fit into your scheme of explanation?

Dr. Jelliffe: That is explicable in the light of newer physiology. In the first place, the proprioceptive responses, the reactive stimulation of a dilated bladder, give rise to certain symptoms. The lesion in tabes, in which we have bladder symptoms, is a characteristic lesion which interferes with the functioning capacity of the autonomic control; that is to say, the newer work on tabes shows how the sympathetic branch of the vegetative system is involved in the syphilitic, tabetic progress, so that there we have what might be called an organic explanation for the bladder symptom; but behind that there still lies the whole psychology of the bladder action, which I mention in my paper here. It is extremely interesting to see how these multiple sclerosis patients with bladder difficulties, try to swing the environment around; they are the fussiest things that ever happened and the whole household is usually standing on its toes in response to a multiple sclerosis patient with bladder difficulties. Hence, the bladder reaction enters into the localization of the involvement of the autonomic fibers supplying the bladder.

Dr. Timme: Are there any further questions?

Dr. Williams: I should like to ask Dr. Jelliffe how he reconciles his action pattern theory with the patchy nature of the lesions which are neither systematic nor vascular in distribution?

Dr. Jelliffe: How do I put the lesion in the action pattern?

I would put it this way: One of my patients upon whom I have worked for ten years, began his multiple sclerosis with a chorioiditis. That chorioiditis, so far as I could find out, was due to a persistent unconscious pull of the external rectus muscles on the right side. Behind that persistent external pull, of course, there was a long nystagmus component and a short rebound nystagmus component, which really did not belong to the nystagmus side of it but belonged to the proprioceptive action of the muscles of the external rectus. Symbolically, this represented a looking-away from guilt. The patient did not want to face a certain situation and was constantly shifting his eye and pulling it away from the situation.

The implantation of the external rectus was the point where the vascular mechanism broke down. That implantation, overstrain with a vascular breaking down, gave rise to certain symptoms. Four years later the patient commenced to develop difficulties in a certain action pattern, which could be correlated with a certain action of the muscles involved in kicking, such as in kicking a football. He had been a great football player at college. His favorite unconscious sport at the present time is kicking everybody in the face, but he does not know it. He would like to kick everybody in the face, the face representing to him, unconsciously, the football. He cannot kick everybody in the face, therefore he has to repress his cravings.

It is interesting to note that the patches, so far as I could work them out by the ordinary senori-motor tests, and so far as one could go into the ordinary technique of determination of the localization of the plaques, did involve that very mechanism—he was prevented from kicking. In that way, I correlate action pattern with the vascular process, with the unconscious.

Dr. Williams: He did not answer the question, because, as Dr. Taylor said, the patches are not vascular in distribution, they do not correspond to the individual distribution of any blood-vessel.

Dr. Jelliffe: How does he know?

Dr. Williams: Because he has examined the post-mortems of those cases.

If unconscious factors are the determinants of patchy sclerosis, why do not patches occur in the prototype of the diseases alleged to be the product of unconscious factors by those who so believe, namely, schizophrenia or dementia præcox?

Dr. Jelliffe: Not to be over-critical of questions, Dr. Timme, I do not really know what the question means, but I am inclined to think that Dr. Williams is asking, Does a patient develop schizophrenia because of an unconscious conflict?

Dr. Williams: That is not the question. The question is: Why does not a schizophrenic patient develop patchy sclerosis?

Dr. Jelliffe: The schizophrenic case does not get the patches. I said in my paper, it would make an interesting series of correlations to show how some people escaped getting these patches by symbolic situations; in other words, I might say, if I so desired, that multiple sclerosis was a schizophrenia of the spinal axis.

Dr. Timme: Are there any further questions?

Dr. Williams: Why does not Dr. Jelliffe wish to include multiple sclerosis as schizophrenia of the spinal axis?

Dr. Jelliffe: I would not mind at all. Terms are to be used, after all, so as to clarify and not to obfuscate conversational interchanges. We throw our terms around from generation to generation, and if we have any intellectual acrobatics which can be used at all, any one term under dissimilar circumstances can be used in precisely opposite ways.

Section III

The Symptoms of the Auditory and Vestibular Apparatus and the Ocular Manifestations of Multiple Sclerosis

The symptomatology of the auditory and vestibular apparatus is presented by Dr. Isidore Friesner of New York City.

The ocular manifestations of multiple sclerosis is considered by Dr. Ward A. Holden of New York City.

Symptomatology of the Auditory and Vestibular Apparatus in Multiple Sclerosis

Isidore Friesner, M. D.

These clinical studies of auditory and vestibular signs in multiple sclerosis are based on the examination of 10 cases in which the diagnosis of this disease had been made.

The examination divides itself naturally into:

1. A determination of the hearing status.

2a. The estimation of the presence or absence of spontaneous signs of disturbances in the vestibular apparatus.

2b. The observation of the character of the responses to experimental vestibular stimulation.

All 10 subjects of this examination had normal middle ears. In none was there any disturbance of hearing, and, further, there was no history of deafness. Transitory deafness, however, does occur as a symptom of multiple sclerosis, and has been reported by Beck in 2 cases. In a 3rd, where the diagnosis was not positive, there were also temporary disturbances in hearing of the nerve type. He believes this analogous to transitory amaurosis, which occurs in multiple sclerosis. Hess, Oppenheim and Marburg have also observed transitory deafness. Bárány has reported a case of multiple sclerosis in which the diagnosis originally was an acusticus tumor. This patient was operated upon, and the tumor was not found. Subsequent to the operation, Bárány reexamined him, and found unilateral total deafness, with loss of nystagmus, following experimental vestibular stimulation, but with normal vertigo and pass-pointing. The original diagnosis of acusticus tumor was based upon the erroneous assumption that the eighth nerve had undergone complete loss of function. The second examination showed the astounding peculiarity that, although nystagmus did not appear as the result of caloric labyrinthine stimulation, vertigo and pass-pointing did. Bárány concludes from this observation that the lesion cannot involve the eighth nerve itself, but must be located in the brain stem beyond the point at which the vestibular fibers have separated into their tracts.

Nystagmus. With regard to the spontaneous signs of disturbances in the vestibular apparatus, the most important, perhaps, is nystagmus. This occurred in 7 of the 10 cases examined. Nystagmus was recognized by the older neurologists as a cardinal symptom of multiple sclerosis, and is considered an important one by the modern neurologists. It occurs in a little over 50 per cent of the cases. In the patients examined by me, spontaneous nystagmus occurred in all directions, that is, to both sides, upwards, downwards, and obliquely. In some cases, several of these were combined.

The spontaneous nystagmus, too, varies in type. As a rule, the lateral or horizontal nystagmus predominates. In one instance, there was a combination of rotatory and horizontal nystagmus. The nystagmus is of two varieties: (1) Oscillations of the eyeball; (2) definitely rhythmic movements. A vertical nystagmus upwards or downwards occurred in 4 of the 10 cases. This is considered pathognomonic of a lesion in the brain stem. One of the striking peculiarities regarding the spontaneous nystagmus is the fact that it frequently persists despite the superimposed induced nystagmus, so that in response to cold caloric stimulation, one may have a normal nystagmus directed to the side opposite to the ear which is stimulated, and yet the spontaneous nystagmus in some other directions will persist, and may even be accentuated. Occasionally it seems as if the spontaneous and induced nystagmus combined and caused most bizarre ocular movements. Another striking peculiarity was the loss of conjugate movements of the eyes, following induced nystagmus. Thus, in 4 instances, as the result of caloric stimulation, both eyes executed nystagmic movements, normal in their direction and plane, but differing in rhythm in the two eyes. Manifestly, the integrity of the mechanism that controls conjugate eye movements is essential to the normal play of induced vestibular nystagmus. In 4 of the 10 cases, caloric stimulation caused a skew deviation, which did not occur spontaneously. In several instances, caloric stimulation was unable to produce definite responses. In one case, caloric stimulation of one set of vertical canals caused no nystagmus whatsoever, but did arouse normal vertigo and normal pass-pointing.

Vertigo. Leidler states that vertigo is a common symptom of multiple sclerosis. In none of the cases observed, however, was there at the time of examination any evidence of vertigo, as determined by the pointing tests. None of the 10 showed spontaneous pass-pointing. In several of the cases, because of the tremendous intention tremor, pointing tests were impossible; but where they were made, the general direction of the arm movement was conserved, the tremor interfering only with the nice approximation of finger to finger. In no instance have I observed the hyper-irritability described by

Bárány. In fact, it has seemed to me that even where the nystagmus, following caloric stimulation, approximated the normal, vertigo was frequently suppressed, and nausea and vomiting never occurred.

It would be exceedingly rash to dignify a discussion of the clinical data here presented, by the term "conclusion," so much still rests upon speculation and so little upon definite knowledge. From these examinations, however, there have sprung certain suggestions which are at least worthy of mention:

1. The usual type of spontaneous nystagmus (namely, rhythmic) combined with the fact that it is frequently not amenable to influences aroused by vestibular stimulation, suggest that the origin of the nystagmus is a lesion in the vestibulo-ocular mechanism.

2. It is certain that as the result of vestibular stimulation, nystagmus and vertigo and pass-pointing may at times be aroused independent of each other. This may be true not only of the static labyrinth as a whole, but may apply also to the individual canals, at least to the vertical canals, as differentiated from the horizontal. These facts suggest a difference in location between the vestibular nuclei or tracts which intermediate nystagmus impulses and those which have to do with the sense of position in space.

3. It appears, further, from Beck's cases, that nystagmus, vertigo and pass-pointing may be aroused by experimental vestibular stimulation, and yet the falling cannot be influenced by changes in the position of the head. This fact suggests a difference in location of the vestibular nuclei or tracts which intermediate so-called vertigo impulses to the extremities, and those which transmit similar impulses to the trunk.

4. The presence of induced nystagmus with the total loss or marked suppression of vertigo, suggests the possibility of extensive disease of the cerebellar nuclei, or of the cerebellocerebral tracts, as the cause of this phenomenon.

5. Finally it is clear that careful clinical study, combined with histological research in cases of multiple sclerosis, will do much to clear up the shadows still overhanging the anatomy and physiology of the central portion of the vestibular apparatus.

The following questions submitted to Dr. Friesner before the Commission, together with the answers to them, are here reported verbatim.

Dr. Strauss: Dr. Friesner, of course, is familiar with the work of Dr. Sachs and his associate, in which they have demonstrated that the vestibulo-ocular pathway, described by Wilson and Pike, apparently does not exist. Would Dr. Friesner, through his study on these cases, offer any suggestion as to where this pathway does lie, because he supposes a connection between the ocular movements and the vestibular nuclei?

Dr. Friesner: The anatomy and physiology of the central portion of the vestibular and aural apparatus change almost as frequently as do fashions. Many years ago when I first began its study, we accepted the work of Kohnstamm and Quensel. I understand that more recently this has been disproved, so that I am quite justified in my assumption that the anatomy and physiology of the central portion of the vestibular and aural apparatus changes almost as often as do the fashions.

Dr. Sachs: For further elucidation, would Dr. Friesner state what he really means by spontaneous; in what sense he employes the term "spontaneous nystagmus"?

Dr. Freisner: The nystagmus that occurs not as the result of experimental labyrinthine stimulation.

I would like to say one word more to Dr. Strauss. It is perfectly apparent from cases of this kind such as I have here, from Bárány's case, for instance, that vertigo, as it results from vestibular stimulation and nystagmus, must of necessity have different pathways in the brain stem, because Bárány, in the report of his case, assumed originally that because nystagmus did not occur as the result of vestibular stimulation, the lesion was in the eighth nerve, and that, with total deafness, made him believe that this patient had an acusticus tumor. Then he was met with the astounding peculiarity that although nystagmus did not occur when the labyrinth was stimulated, vertigo occurred in the normal planes and this vertigo was evidenced by a normal past-point.

In a patchy disease such as multiple sclerosis, it is a perfectly rational assumption that those impulses which had to do with nystagmus, as the result of vestibular stimulation alone, were hit, whereas those that had to do with a change in the sense of position were normal and permanent.

Dr. Hunt: Dr. Friesner, do you make a distinction between a nystagmus of cerebellar origin and of vestibular origin, and how would you distinguish them?

Dr. Friesner: Dr. Hunt, I am not sure that there is a nystagmus of cerebellar origin. Now that may be heresy, but I am not at all sure that there is such a thing. Dr. Strauss will substantiate this statement because he too, has seen this thing: In one case I have been able to demonstrate that skew deviation, which has been considered a definite sign of a cerebellar lesion, occurs as the result of vestibular stimulation. Surely the fibers that have to do with the intermediation of these impulses have nothing to do with the cerebellum. Perhaps this form of oscillation that occurs with the rhythmic nystagmus may be cerebellar (I do not know), but a vestibular nystagmus that is of vestibular origin—and by vestibular I include not only the periphery but also the tracts and the nuclei—that nystagmus has a very definite type; it is rhythmic.

Dr. Hunt: Do you recognize in both forms, or in all these forms of nystagmus, a slow and a rapid component?

Dr. Friesner: That is the significance of rhythmic.

Dr. Hunt: And that you associate with the cerebellum rather than with the vestibular apparatus?

Dr. Friesner: No, with the vestibular apparatus.

Dr. Dana: What subjective symptoms are caused by nystagmus, if any? That is one question. Is there any subjective symptom that is characteristic of the different kinds of nystagmus?

Dr. Friesner: I think much would depend upon the origin of the nystagmus. For instance, in a nystagmus of peripheral origin, where an eighth nerve or a labyrinth is involved, there is a certain degree of vertigo that is due to the nystagmus; that is, these patients when they open their eyes see objects about them apparently revolving in the direction of the rapid phase of the nystagmus.

Dr. Dana: And they make this as a general complaint to the doctor or to the neurologist (they do to me, for example): That they are uncomfortable; they cannot see well. That is what I refer to. They have definite subjective symptoms sometimes as the result of the nystagmus, do they not?

Dr. Friesner: Yes, but my impression is that these occur only early in the disease of the central nervous system.

Dr. Dana: Is there any difference in the vertical or the horizontal or the rotatory nystagmus?

Dr. Friesner: I can answer that only by the analogy of what occurs as the result of experimental stimulation. The rotatory nystagmus causes the greatest degree of vertigo. Objects there would be upset, as it were, and not moving laterally on a horizontal plane.

Dr. Taylor: Would you regard the generally accepted horizontal nystagmus as more frequent than the vertical in multiple sclerosis; and, if so, would you regard that as of any diagnostic value? Do you think that the lateral or horizontal nystagmus is more frequent in multiple sclerosis than the vertical as ordinarily accepted?

Dr. Friesner: I do not think my clinical experience with multiple sclerosis is sufficient to answer that question. The lateral nystagmus surely is a more common type of nystagmus than the vertical. Whether that is true with multiple sclerosis or not, I do not know.

Dr. Sachs: May I say that in 99 cases examined, we had the horizontal and vertical nystagmus in 17 cases; the horizontal and rotatory in 3 cases.

Dr. Friesner: Then the percentage of vertical nystagmus in my series is rather high, is it not? Four out of 10 had vertical nystagmus upward or downward.

Dr. Sachs: Most of the cases that I examined had had this disease for a considerable period of time, over a number of years. One of them had multiple sclerosis for over thirty years. Whether through the progress of the ailment the brain stem had become definitely involved so as to cause the vertical nystagmus, I do not know, but that is quite possible as a means of explanation.

Dr. Kennedy: In the discussion between Dr. Sachs and Dr. Friesner, Dr. Friesner made the remark that he used the term "spontaneous nystagmus" meaning a nystagmus obtained without stimulation. It is unfortunate that this term is already in the literature. Dr. Friesner also named a nystagmus which occurs when the eyes are not deviated upward, downward or laterally; it would be unfortunate, I think, to use the term "spontaneous nystagmus" in that case. Perhaps Dr. Friesner could use the term "unstimulated nystagmus."

Dr. Friesner: Pike has shown (and we have found it to be true) that in very many instances where the nystagmus is of central origin it does not appear except on fixation and on movement of the eyeball in the plane in which the nystagmus occurs. For instance, there are many patients with central lesions who have a vertical nystagmus upward only when they fix on the finger held high above the head. As they look straight ahead, there is no nystagmus, but there is a vertical nystagmus nevertheless and it is a spontaneous vertical nystagmus. At all events, that nomenclature has crept into the otological literature to such an extent that I doubt very much whether substitution for it could be made.

Dr. Sachs: You simply mean that it is non-experimental.

Dr. Friesner: Exactly.

Dr. Tilney: Dr. Williams asks: "Do you regard the absence of provoked vertigo as due to supranuclear lesions?"

Dr. Friesner: Well, supranuclear lesions as I understand them, if they had something to do with the suppression of vertigo, would have to be bilateral, that is, somewhere in both temporal lobes, or in the pathway to the temporal lobes. We do not know just what the pathway is of those fibers that have to do with the impulses which give us the consciousness of change of position. We have found, however, in an amount of clinical material far too insufficient to draw conclusions from, that cerebellar disease, particularly in the nuclei, does interfere with those impulses that we have called vertigo impulses; that disease, for instance, in the superior cerebellar peduncles or in the midbrain, has interfered with the vertigo, vertigo being entirely suppressed, and we have attempted, as I have said before, on quite insufficient clinical grounds and practically no pathological basis at all, to draw the conclusion that vertigo impulses are intermediated by the cerebellum. Whether that be true or not, we do not know. Extensive nuclear disease in the cerebellum or in the region of the superior cerebellar peduncles would interfere with what we have called vertigo impulses.

Dr. Timme: Is there any proof that nystagmus caused by vestibular stimulation is not due to stimulation of the cerebellum via the vestibular pathways?

Dr. Friesner: I think there is. I cannot recall the literature accurately, but I believe that somewhere back in my mind there is the work of total extirpation of the cerebellum in the dog, with subsequent destruction of one labyrinth and a normal *ausfalls* phenomenon, that is, normal in the sense that the usual pathological nystagmus occurred, so that we have the experimental proof—I am positive of this—that the cerebellum in no way intermediates impulses that have to do with nystagmus, so far as the vestibular apparatus is concerned.

The Ocular Manifestations of Multiple Sclerosis

Ward A. Holden, M. D.

Pupillary anomalies in multiple sclerosis are rare. Palsies of the ocular muscles are found in but 20 per cent of the cases, are of nuclear origin, are frequently transitory and have no features which are characteristic. Nystagmus or nystagmoid twitching is found in almost all advanced cases.

Our particular interest, then, lies in the consideration of the less easily interpreted optic nerve symptoms, which are of importance, first, in assisting in the diagnosis of multiple sclerosis, and second, in enabling us to make a prognosis that will relieve the patient of the fear of impending blindness. The optic nerve symptoms of multiple sclerosis have long been known and the chief advance in our knowledge of them, recently, has been in the greater precision in determining the defects in the visual field and in the earlier recognition of the symptoms as being dependent upon the disseminated disease of the central nervous system.

A paper I read in 1908 on the subject before a joint session of the ophthalmological and neurological sections of the American Medical Association (*J. Am. M. Assn.*, li, No. 2) was illustrated with drawings of the discs and charts of the corresponding fields in the different types of visual disturbance, and also with photomicrographs showing degeneration of the axial portions of the optic nerves in cases with central scotoma. At that time the ophthalmologist on finding a central scotoma was sometimes content to make a diagnosis of retrobulbar neuritis without going very deeply into its etiology. The purpose of that paper was to show that a central scotoma of rapid onset, if one could exclude poisoning by chemicals, diabetes, retinal lesions and hysteria, meant as a rule one of two things—either pressure upon the optic nerve from retained secretion in the paranasal sinuses, or multiple sclerosis. A rhinological examination with radiograms of the sinuses will exclude the sinus origin, except in the rare cases in which sclerotic conditions of the sinuses may underlie the trouble. In some of these latter conditions exposure and aeration of sinuses without retained secretion have been followed by improvement in vision. After exclusion of the sinuses and the other factors mentioned, it is justifiable to make a diagnosis of multiple sclerosis if one or more additional symptoms of that disease can be elicited. But since the visual disturbances are sometimes the earliest symptoms to appear, the opthalmologist whom the patient consults may be puzzled and the neurologist's examination will not always confirm his tentative diagnosis.

One of the most important of recent papers on the subject is that by Klingmann (*J. Nerv. and Ment. Dis.*, 1912, No. 12). He gives in detail the histories of 12 patients with unquestionable multiple sclerosis in which visual disturbances were noted early. The most illuminating and novel feature of his paper is the record of the visual fields. His fields taken carefully with very small test objects show in many cases very small absolute multiple scotomata in or near the point of fixation and rather more numerous in the temporal than in the nasal portion of the field. With his small test objects he found as many as sixteen small *absolute* scotomata in cases in which earlier examiners might have noted only a large diffuse *relative* scotoma.

The symptoms on which Klingmann insists as corroborative of the diagnosis of multiple sclerosis when a central scotoma is found are ankle clonus and the Babinski toe reflex. It is surprising that in no case history does he mention the state of the abdominal reflexes. Yet diminished abdominal reflexes are found in multiple sclerosis as frequently as the Babinski reflex, namely, in about 80 per cent of cases. And we now have learned that if the other common causes of central scotoma can be eliminated, diminution of abdominal reflexes warrants us in diagnosing multiple sclerosis, even if no other symptoms are present. And often no other symptoms appear for years.

The Optic Nerve Changes. The characteristic plaques develop in the optic nerve or tract at any point, but with great frequency in the axial fiber bundle of the optic nerve. The axones from the ganglion cells in the macular region of the retina—the center of distinct vision—run in the temporal portion of the optic disc and farther back in their course reach the center of the optic nerve to form the so-called axial bundle. This is a sensitive bundle which is particularly affected by toxic agents and by diffuse pressure upon the optic nerve.

In the plaque the inflammatory exudation at first merely compresses the optic nerve fibers and interferes with their function. Later the medullary sheaths break down and the glia tissue proliferates, but since the axis cylinders are not destroyed restitution of vision frequently takes place. In the

beginning, if the inflammatory plaque lies near the optic disc, there may be congestion or a low degree of edema of the disc, but if the plaque lies far back in the nerve the disc for a time appears normal. However, after an interval, ranging from one to six weeks, pallor of the disc usually appears and remains permanently, even though vision is restored to normal again.

The pallor of the disc varies with the extent and location of the plaques and for descriptive purposes it has been classified as of three varieties: (*a*) A pronounced whiteness of the disc in its entire extent; (*b*) a slight pallor of the disc in its entire extent, and (*c*) a pallor of the inferotemporal third of the disc with the other two-thirds normal in color.

The first and second varieties—diffuse pallor—are found also in tabic and other general atrophies, while the third—temporal pallor—indicates an involvement of the axial or papillomacular bundle alone. This is the variety of pallor frequently found in multiple sclerosis and it is, to a certain degree, characteristic of this disease.

In some cases there is considerable difficulty in interpreting pallor of the optic disc. In health, its temporal half is always paler than its nasal half and occasionally in healthy persons with normal vision one disc is distinctly paler than the other. Furthermore, in some cases of multiple sclerosis pallor of the temporal half of the disc is found while vision is still normal. This suggests either that there may have been a slight involvement of the nerve which had not yet disturbed its function, or, that there may have been earlier disturbances in the field of vision of which the patient had not been conscious and from which recovery had taken place. The appearance of the optic disc, therefore, has less diagnostic significance than the acuteness and the fields of vision.

The Fields of Vision. The defective fields in multiple sclerosis are of three types: (*a*) Peripheral contraction; (*b*) central or paracentral scotoma, and (*c*) a combination of both peripheral and central defects. Many observers find peripheral contraction with considerable frequency, but it is quite certain that in a number of these cases the defect is of functional rather than of organic nature. We have been

accustomed to speak of a peripheral contraction, often increasing as the test continues, as a functional or fatigue field which is found in the neurasthenic or hysterical. The present-day interpretation of this fatigue field is that it is suggested by the examiner to a patient susceptible of suggestion. In multiple sclerosis the mental state of the patient is often one in which suggestions are readily seized upon. Hence, while at times there may be definite constant peripheral defects in the field due to a lesion in the optic nerve, we yet view with suspicion records of a more or less uniform contraction of the entire periphery of the field and regard many of these contractions as being of a functional nature and suggested to the patient through defective technique in taking the field.

The more characteristic defects in the field are the central and paracentral scotomata. In these cases again great care must be taken in the tests which must be carried out quickly with very small test objects, for the patient soon becomes confused and his answers contradictory. When there are very small absolute and larger relative defects, no 2 observers may obtain identical fields. In case of paracentral scotomata the patient may be aware of disturbed vision while his central acuteness of vision is normal with the test cards, and some searching may be required to find the small defects in the field that the pallor of the disc leads us to suspect.

The combined form of peripheral contraction and central scotoma is not infrequent. Here, too, a distinction must be made between the functional and the true defects. In advanced progressive cases almost every form of field may be found, even homonymous hemianopsia.

Course and Diagnosis. The onset of the visual disturbance is acute in half the cases and in a large percentage both eyes are affected. The maximum disturbance of vision may be reached in a few days and recovery may take place in an equal time. Again the disturbance of vision may long remain stationary, then either improve or grow worse, and remissions, relapses and extensions may alternate for years. With a central scotoma the patient cannot read, but he can go about without difficulty, and unlike atrophies of the optic

nerve of other origin this variety never leads to blindness, and a reassuring prognosis may always be given.

When the visual disturbance is the first symptom noticed and a central or paracentral scotoma develops within a few days without pallor of the disc, the differential diagnosis between multiple sclerosis and hysteria is often most difficult. The patient with multiple sclerosis may exhibit hysterical manifestations and an adequate psychic trauma may be discovered. The vision may improve slowly, or remain stationary, but after a lapse of weeks a pallor of the disc appears which confirms the diagnosis of organic disease.

There is no difficulty in distinguishing between the optic nerve disturbances of multiple sclerosis and those of tabes. It may be difficult, however, to distinguish between them and those of disseminated myelitis in the rare cases in which visual symptoms of myelitis precede the spinal symptoms. In my own observations of disseminated myelitis, however, the visual disturbance in half the cases conformed to the type of lateral hemianopsia in the field of one eye only, which is very rare in multiple sclerosis.

In summing up we may say that defective vision in one eye or both, generally of acute onset and mostly with one or more small scotomata in or near the point of fixation, is a common symptom of multiple sclerosis that may come on at any time, but often appears early in the disease. A rhinological examination should exclude the paranasal sinuses as causative factors and then in many cases we must exclude hysteria.

The following questions submitted to Dr. Holden before the Commission, together with the answers to them, are here reported verbatim.

Dr. Patrick: Dr. Holden said there might be this pallor of the disc, especially the lower temporal third, without diminution of vision. I assume that that statement includes normal fields?

Dr. Holden: Yes.

Dr. Patrick: Has Dr. Holden ever seen optic neuritis as a manifestation of multiple sclerosis? I should like to make that a little more distinct. I do not mean a varying of the disc, which might be questionable and concerning which there might be a difference of opinion; I mean a distinct swelling.

Dr. Holden: I think every textbook will say that papilledema is found in multiple sclerosis. I never have seen it and I have examined a number of cases. In some cases we get a slight blurring of the margin. Personally, I never have seen anything that I should have called optic neuritis or papilledema.

Dr. Sachs: Are we right then in stating that the pallor, as found in multiple sclerosis, never leads to amblyopia.

Dr. Holden: It practically never leads to complete blindness. In the literature there are perhaps 1 or 2 cases. Most of us have never seen a person completely blind. A central scotoma may become quite extensive, but there is always sufficient field of vision in one eye for the patient to see enough to get about.

Dr. Dana: I would like Dr. Holden to tell us whether he thinks the lesions that he sees, the phenomena that he sees about the eye, are suggestive of toxic or inflammatory conditions on the whole? Would you say that the condition which is causing these various ocular manifestations has more the character of a toxin or of an inflammatory process?

Dr. Holden: The fact that there is redness of the disc in some of the cases and occasionally a little blurring, would rather suggest an inflammatory process in the plaque. That is all the evidence we have, one way or the other, so far as I know. The appearance of the disc in which the plaque lies near it, would rather suggest that it was inflammatory to a certain extent.

Dr. Campbell: I should like to ask Dr. Holden whether visual hallucinations have played any rôle in the symptomatology in his patients? I ask it in view of a case of a patient where a diagnosis of multiple sclerosis was made.

Dr. Holden: I do not think so. I do not remember having my attention called to that. The only cases I recollect of distinct visual hallucinations have been in tumors involving the optic radiation far back; then we are very apt to have hallucinations in one-half of the visual field, but I have never had my attention called to visual hallucinations in multiple sclerosis.

Section IV

The Symptoms Referable to the Visceral Nervous System and the Glands of Internal Secretion, the Spinal Fluid and Blood in Multiple Sclerosis and the Bacteriological Investigation of Multiple Sclerosis

The relation of multiple sclerosis to disorders of the visceral nervous system and glands of internal secretion, is presented

by Drs. Walter M. Kraus and Irving H. Pardee of New York City.

The studies on the cerebrospinal fluid and blood in multiple sclerosis are described by Drs. James B. Ayer and Harold E. Foster of Boston. The subject of experimental investigation with the object of corroborating the work of other investigators or shedding new light upon the problem, is discussed by Dr. Oscar Teague of New York City.

The Relation of Multiple Sclerosis to Disorders of the Visceral Nervous System and the Glands of Internal Secretion

Walter M. Kraus, M. D., and Irving H. Pardee, M. D.

Introduction. Quite contrary to what might be expected on casual consideration the clinical manifestations of involvement by multiple sclerosis of the visceral nervous system and its end organs are very limited. The pathology of the condition in the spinal cord and brain stem would lead to the belief that both the primary visceral paths arising above the midbrain and extending into the spinal cord, as well as the secondary or preganglionic paths arising segmentally in the spinal cord, would, by involvement, yield very readily appreciable clinical manifestations. This is rarely the case. The reason for this lies, in all probability, in the fact that the peripheral portions of the visceral nervous system present a certain automaticity when cut off from their central connections. In very acute stages of the disease, some visceral manifestations may be present, such as tachycardia, paralysis of the bowels and bladder disorders.

The Thyroid. The thyroid, as shown by the examination of moderately well-advanced cases, showed evidence of being underactive in a large proportion of these. This was shown by the presence of scaling, dryness of the skin, falling out of the eyebrows and hair. Since these patients had not been examined prior to the onset of the disease the preexistence of these anomalies cannot be ruled out. However, it seems probable that this condition of impaired metabolism may be due to the chronic nature of the disease. No evidences of disturbances of the other glands of internal secretion were

found which could be attributed to the disease. This does not mean that disturbances were not found. However, they were not uniform and could not be shown to be causally related to the disease.

The Pupil. Any consideration of the condition of the pupil demands that syphilis be excluded. In 10 of 12 cases, examination has not shown any change in the form, size or reaction to light or accommodation of the pupils. In 2 cases the pupils were small and reacted very slightly to light or in accommodation. Differences in the size of the pupils due to differences in the extent of the atrophy were not noted (such differences have been reported).

The Heart. In over half the cases examined, the pulse rates as charted in the nurse's records showed a tachycardia. In the same number of cases the pulse rate, as examined by us, was found increased considerably above normal (up to 120 per minute). The elements of emotion in this examination must be considered.

To state, on the basis of an isolated count or the nurse's records, that the pulse rate is increased, appears to the writers as hazardous. The possibility of increased lability of reaction due to this disease of the central nervous system must be borne in mind. It seems true, however, in spite of the conservative stand taken that, in the acute stages of the disease or its remissions, there may exist a tachycardia, manifested by a pulse rate as high as 120. This was shown in a case recently dead of pathologically proven multiple sclerosis.

Sphincters. No subject in neurology is more difficult than that of the control of the bladder and of its sphincters. The visceral nervous system unquestionably controls the bladder musculature, while the voluntary nervous system controls the musculature of the sphincters. The frequency with which bladder disturbances are found in multiple sclerosis requires no emphasis. However, it seems very difficult to decide whether these disturbances are due to an involvement of the voluntary or involuntary muscles. On the assumption that there is a blocking off from the central nervous system in multiple sclerosis, automaticity of the bladder might result. In some cases there is evidence

of paralysis of the bowels, varying in degree of severity. The milder forms of paralysis are manifested by constipation. Since the control of the bladder and the bowel by the visceral nervous system is very similar, these bowel paralyses may be used as an argument that multiple sclerosis affects the visceral centers controlling both the bowel and bladder

Conclusions. At the present time it seems most probable that visceral manifestations occur mainly in the acute stages of the disease. There seem to be evidence of paralysis rather than of irritation. When the acute stage has subsided there seems to be a return to normal, possibly due to the automaticity previously mentioned. Pupillary changes may exist in the chronic stages of the disease. It is possible that visceral disturbances are present in a form so mild as to be clinically indeterminable by the ordinary methods of examination. We have not observed them, however. Clinical disorders attributable to the glands of internal secretion, and causally related to the disease, have not been observed.

The following questions submitted to Dr. Pardee before the Commission, together with the answers to them, are here reported verbatim.

Dr. Strauss: I would like to ask Drs. Kraus and Pardee whether in the thyroid cases they have studied the basal metabolism, whether they have taken into consideration the sugar tolerance; whether they have made tests in those cases?

Dr. Pardee: In the cases that we have examined, which have shown evidence of clinical thyroid disturbance, there were no basal metabolism tests made and no sugar tolerance tests made, because the majority of the cases we saw were in hospitals where that could not be carried out.

Dr. Strauss: Was the Goetsch test made?

Dr. Pardee: No.

Dr. Strauss: Did the gentlemen make any blood counts, to see if there was any lymphocytosis in those cases?

Dr. Pardee: A considerable number had blood counts made and there was no evidence of any lymphocyte changes or polynuclear changes; no lymphocyte increases in any of these cases.

Dr. Timme: May I ask Dr. Pardee, whether he noticed any muscular atrophies of the progressive type, as in the cases reported on the Continent?

Dr. Pardee: In the cases we examined, there were none that showed any muscular atrophy other than those that would be expected from that type of bedridden patients.

Dr. Timme: How many cases of multiple sclerosis did the gentlemen examine?

Dr. Pardee: We examined in all about 12 cases in minute detail for endocrine disorders.

Dr. Timme: Were all in the chronic stage?

Dr. Pardee: All were in the chronic stage except one.

Dr. Timme: What were the blood pressures, Dr. Pardee?

Dr. Pardee: The blood pressures showed considerable variability; they varied between 90 and 120.

Dr. Timme: Was there any sign of involvement of the sympathetic system in so far as a pigmentation or a bronzing of the skin indicating a disturbance of the suprarenal cortex?

Dr. Pardee: There was 1 case which showed two patches of pigmentation on the body, but we did not feel we could attribute that to the disease in any way, that being a rather common thing in many cases that have not multiple sclerosis.

Dr. Timme: You do not know whether the patches preceded or succeeded the onset of the disease?

Dr. Pardee: No. I do not.

Dr. Barker: I would like to ask if any of these patients, these 12, showed any peculiarity of external habitus; that is, was the distribution of the hair or the bony constitution at all suggestive of queer pituitary make-up, or suprarenal make-up; did they look like ordinary American citizens, or had they a peculiar habitus?

Dr. Pardee: There were 2 cases which showed the usual appearance which is characteristic of the thymic make-up, the smooth skin. There was another case which was a very marked pituitary type, which showed considerable spaces between the teeth, heavy eyebrows and considerable obesity, particularly below the waist; but there was no one type which ran through all the cases. Each case, from the standpoint of its clinical endocrine type, was one in itself, and there was no striking endocrinal anomaly which ran through all the cases.

Dr. Barker: Would you say, taken as a whole, they showed any greater difference in external habitus than any other patients that you would see?

Dr. Pardee: No, I would say they were the general patients that one would see in almost any other organic disease.

Dr. Dana: Were they over-fat?

Dr. Pardee: The pituitary case I mentioned was quite obese. She was about forty-five years of age and had extremely small

hands, and the other characteristics which I mentioned to Dr. Barker.

Dr. Dana: I have never seen a fat case of multiple sclerosis.

Dr. Pardee: It was an unquestionable case at the Montefiore Hospital. It was a noticeable pituitary obesity. The weight was distributed below the chest.

Dr. Timme: Do you gentlemen feel that you have covered the ground sufficiently in the examination of 12 cases to exclude any endocrine symptomatology or any endocrine influence in the progression of the disease?

Dr. Pardee: Yes, we do.

Dr. Timme: How do so-called thyroid deficiency symptoms, which you have found, compare in frequency with the occurrence of these symptoms in other persons of the same age? The gentleman who asked this question comes from Pittsburgh, and I am of the opinion that a great many more of these cases are seen there than we see here on the coast.

Dr. Pardee: I have no statistics as to either the presence of a hypothyroidism in multiple sclerosis or in the average patients as we meet them in the clinics or in the hospitals; hence I feel it would be quite impossible to answer that in a definite way. I should think probably 4 or 5 of the 12 cases showed evidence of a hypothyroid state, from the clinical examination.

Dr. Timme: There were no bony abnormalities of the spinal column?

Dr. Pardee: No, sir.

Dr. Timme: There was no increase in the number of vertebrae?

Dr. Pardee: No.

Dr. Timme: There were no anomalies of the bony structure whatever?

Dr. Pardee: This pituitary case showed anomalies of the bony structure; otherwise there were none.

Studies on the Cerebrospinal Fluid and Blood in Multiple Sclerosis

James B. Ayer, M. D., and Harold E. Foster, M. D.

In a disease presenting such marked pathological changes as multiple sclerosis, one might confidently expect abnormalities, perhaps characteristics, in the cerebrospinal fluid. Yet a review of the literature up to 1909 fails not only to reveal findings pathognomonic of the disease, but shows that many authors regard the fluid as essentially normal. Eskuchen

(1919) states that 50 per cent of fluids are entirely normal; of the 50 per cent abnormal, increase in pressure, pleocytosis and a strong globulin reaction are found, and in 20 per cent the "paretic" goldsol curve.

Aside from pleocytosis in some cases, never very high; a globulin increase in some cases, seldom great; and a goldsol reaction in some cases, not infrequently in the "paretic zone," no writer claims changes which can be construed as indicative of multiple sclerosis, certainly not pathognomonic.

PERSONAL OBSERVATIONS

The writers were able to collect 38 cases personally known to one or both of them from clinical or laboratory aspect. Many of these patients have been followed for a number of years and all show a clinical picture which admits of little doubt as to the diagnosis of multiple sclerosis. Fourteen of these were males, 24 females.

Character of Fluid. The fluid was invariably clear, colorless and without clot.

Pressure. This was measured in a number of the patients by allowing fluid to flow into a 2 mm. bore glass manometer. Readings were never above the limit of normal, were usually in the mid-normal zone, but frequently were low. There was nothing in the character of pulse and respiratory oscillations to cause comment, and when jugular compression was employed the rise of pressure was prompt, indicative of absence of meningeal or other block in the spinal subarachnoid space.

Cells. Fifty-one counts in 36 patients. The cell count may be briefly summarized as follows:

0– 5 cells	29 counts
6–10 cells	8 counts
11–20 cells	8 counts
21–30 cells	2 counts
42 cells	1 count

Total Protein. This was estimated by a number of tests, but during the past two years by a quantitative method. Where this latter method was employed the readings were

usually found to be just below the high normal limit of 40 mg. per 100 c. c.; the highest, 111 mg., the lowest 22 mg. Taking all of the tests into consideration, one-half of the cases show protein increase, never of high degree.

Globulin. Tests were made almost exclusively by means of the ring test with saturated ammonium sulphate (Ross-Jones modification of Nonne). Of 31 patients in which this examination was made, 22 gave a negative, and 9 a positive reaction. The globulin ring was never a conspicuous one, and never approached the density commonly seen in general paresis.

Wassermann Reaction. This reaction was negative throughout in every case. One weakly positive reaction in a patient presenting on two other occasions negative reactions, one anticomplementary, and one unsatisfactory (unexplained) reaction are exceptions which do not seem to vitiate the diagnosis in these cases.

Gold Chloride Test. The tests in 1914 1917 were performed under the direction of Dr. W. A. Hinton by a method described by him; those of 1920 and 1921 by one of us (Foster) by the following method: To 1,000 c. c. of triply distilled water in an Erlenmeyer flask (Pyrex) is added, at 60° C., 6 c. c. of a 2 per cent aqueous solution of potassium carbonate; immediately is added 10 c. c. of a 1 per cent aqueous solution of gold chloride (acid). A Meaker burner is then substituted for the Bunsen burner and the temperature rapidly raised to 90° C., when 6 c. c. of a 1 per cent solution of formalin is added drop by drop, agitating the flask continuously. The flask with its colorless contents is then removed from the flame and gently rotated until a bright cherry-red color, with a light golden sheen, appears, which is usually after three minutes, but before six or seven minutes. Merck's purest chemicals are used.

Forty-two gold chloride readings are available, obtained in 33 patients. The results may be summarized as follows:

So-called "paretic" type	21 fluids in 16 patients
So-called "luetic" type	7 fluids in 7 patients
Other positive reactions	3 fluids in 3 patients
Negative reactions	11 fluids in 10 patients

It will be seen from this table that the "paretic" type was found by us in 50 per cent of all fluids, and also in nearly one-half of the patients in whom this test was applied.

Sugar. Fourteen findings are recorded. The highest is 0.088 per cent, the lowest 0.048 per cent; the average 0.068 per cent. The method employed was that described in a recent paper (Foster, H. E.; Hyperglycorachia in epidemic encephalitis. *J. Am. M. Assn.*, 1921, lxxvi, 1300) a modification of the Folin-Wu technique for blood.

Non-protein Nitrogen. Of the 11 determinations by the Folin-Wu method, one was too low to read. The lowest readable was 16.9 mgr. and the highest 40.7 mgr. per 100 c. c. The average is 21.5 mgr.

Chlorides. The highest of 11 determinations was 746, the lowest 651, with an average of 688 mgr. per 100 c. c. The technique was that described by Whitehorne.

Acetone Bodies. No evidence of acetone bodies, B-hydroxybutyric acid, aceto-acetic acid and acetone, was found in any of the 9 examinations, using the mercuric sulphate method of Van Slyke-Fitz.

Creatinin. The average of the determinations was 1.78 per 100 c. c.

Urea. In one of the 6 determinations a very slight trace only was found. The average was 15.5 mgr. per 100 c. c.

Uric Acid. Although a slight trace was present in all of the specimens examined, the amount was too low to read.

Creatinin, urea and uric acid were tested for by the methods of Folin-Wu.

OBSERVATIONS ON BLOOD

While the primary object was the study of the cerebrospinal fluid it seemed wise to correlate the blood findings on specimens taken at the same time as the fluid. Whenever the amount of blood taken was sufficient a Wassermann test was made. However, either at this time or at some other, all of the 38 patients have given negative blood Wassermann reactions.

Sugar. All determinations were well within the normal limits, averaging 0.096 per cent.

Non-protein Nitrogen. One reading was slightly higher than normal, 2 were low normal, but the average was 28.1 mg. per 100 c. c. (Normal 25–35).

Chlorides. Highest 622, lowest 404, with average of 490.8 mgr. per 100 c. c.

Acetone Bodies. None.

Creatinin. The highest reading 1.91, the lowest 1.39, the average 1.73 mgr. per 100 c. c.

Urea. High 26.1, low 1.42, average 17.8 mgr. per 100 c. c.

Uric Acid. The results of 5 examinations range from 1.4 to 2.8 mgr. per 100 c. c.

The methods employed in blood analysis were the same as used in the case of the spinal fluid, with the exception that the Folin-Wu method without modification was employed in determining blood sugar.

Discussion. A study of the above cases shows that when all tests on the cerebrospinal fluid are considered it cannot be said that the fluid is entirely negative, except rarely. It is true, however, that the abnormalities may be so slight as to be of little clinical significance except as evidence that some pathology exists. But in approximately half of the fluids there are pathological changes which cannot be overlooked. Foremost of these significant findings is the presence of a "paretic" goldsol curve. Formerly thought to be indicative of general paresis, this reaction has occasionally been found in brain tumor, encephalitis, acute alcoholism, etc. In this laboratory we have rarely seen it except in parenchymatous syphilitic disease of the nervous system and in multiple sclerosis. Another test appears to be of value when considered with the others; a reliable quantitative test shows the total protein of the fluid to be normal or only moderately increased, usually much less than in the various syphilitic affections of the nervous system, with which this disease is likely to be confused. The cell count is usually low, and less than 10 per c. mm., but being mostly lymphocytes the cell picture frequently indicates a mild inflammatory or irritative process.

Is there any reason for these variable types of reaction? Analysis as to the activity of the pathological process might give the clue. Although difficult to be sure of the activity

of a pathological process from clinical observation in any disease, we are confronted in such a consideration in this disease by the fact that we do not even know what the active process looks like. In spite of this fact it seems reasonable to analyze our cases in the following manner. If there has been marked progression in the symptoms, or evidence of invasion of new areas of the nervous system within six months of the time of the examination of the fluid, these cases have been considered as "progressive"; otherwise, "stationary." Analysis of this series with reference to the four tests giving abnormal findings yields the following:

TABLE I

	Progressive	*Stationary*
Total protein		
Increase (over 40 mgr. per cent when quantitated)	14	8
Normal	14	8
Globulin		
Present	8	3
Absent	17	8
Cells		
More than 10 per c. mm.	8	0
Less than 10 per c. mm.	21	16
Gold chloride		
"Paretic" type	16	1
"Luetic" type	5	2
Abnormal reaction	2	1
Negative	3	7

In the above table when 2 or more examinations have been made on 1 patient, only 1 has been recorded unless the type of reaction differed.

It is obvious from analysis of Table 1 that the total protein and globulin are not increased with certainty in either group and that no dependable guide as to the activity of the pathological process is to be gained from these tests. The cell count is perhaps of some value, in that significant increase is found only in the progressive types; however, a much larger number of fluids from actively advancing cases give cell counts below than above 10 per c. mm. Pleocytosis cannot therefore be considered a reliable criterion of activity. Turning to the gold chloride reaction, we are struck

TABLE II

No.	Sex	Age	Date	Site of puncture	Cerebrospinal fluid: Press.	Cells	Alcohol Ppt.	Trichloracetic	Total protein, Mg, per cent	Am. sulph.	Wassermann	Gold chloride	Sugar	N. P. N.	Chlorides	Acetone	Creatinin	Urea	Uric acid	Blood: Wassermann	Sugar	N. P. N.	Chlorides	Acetone	Creatinin	Urea	Uric acid	Symptoms
1		29	1915	Lumbar		4	sl. +				−	0123000000								−								Symptoms 2 yrs. Progressive.
2		28	1921	Lumbar	90	2	0		28	0		5432100000																Symptoms 8 yrs. Mod. progressive.
3	I	23	1920	Lumbar	100	8	+			+	−	5554430000								−								Symptoms 2½ yrs. Mod. progressive.
4	I	40	1921	Lumbar		4	sl. +		38	sl. +	−	5555542100																Symptoms 1 yr. Progressive.
5	I	23	1920	Lumbar	70	6	0		38	0	unsat.	5553210000								−								Symptoms 3 yrs. Progressive.
6	I	23	1920	Lumbar	85	7	0		50	0	−	4443211000								−								Symptoms 4½ yrs. Progressive.
7	I		1920	Lumbar		12	0			0	−	5553100000								−								Symptoms 5 yrs. Progressive.
8	I	4	1920	Lumbar		8	0		47	0	−	5555531000								−								Symptoms 2½ yrs. Progressive.
9	I		1921	Lumbar	50	0	0		24	0	−	5543210000	0 054							−								Symptoms 3 yrs. Slowly progressive.
10	M	33	1920	Lumbar	70	0	+		34	0	−	5555321000	0 069							−								Symptoms several yrs. Slowly progressive.
11	M	33	1921	Lumbar			sl. +		93	0		5554210000								−								Symptoms 30–35 yrs. Stationary.
12		33	Apr., 1921	Cistern	80	2	0		22	0		0000000000								−								Symptoms 6 yrs. Mod. progressive.
13			Apr., 1921	Lumbar	80	2	0		42	0	−	0011100000																
14			Nov., 1921	Cistern		0	0		28	0	−	5555500000	0.065	28.5	695	0	1.25	24 3	tr.	−	0 099	40 0	465	0	1 39	26 1	2 8	No change since previous exam.
15			Nov., 1921	Lumbar		1	0		29	0	−	5555521000	0.067	18 −	686	0	1 20	17 5	tr.									
16			Apr., 1920	Lumbar	60	20	+			+	wk. +	5555532000	. . . .							−								Symptoms rapidly progressive 1½ yrs.
17			May, 1920	Cistern	110	12	sl. +		100	0	−	5555542000																
18			May, 1920	Lumbar		30	+		111	sl. +	−	5555421000																
19			Nov., 1921	Cistern	120	19	0		22	0	−	5555421000	0.048	25 5	701	0		21 1	tr.		0 100						1.9	Progressive.
20			Nov., 1921	Lumbar		18	sl. +		42	0	−		0.058	17 0	693	0		15 9	tr.									
21			1921	Lumbar		1	0		69	0	−	0115322000	0.088	.					.	−								Symptoms 10 yrs. Stationary.
22	I		1921	Lumbar	150	0	0		30	0	−	0001211000	0.067	40.7	651	0	2.38			−		26 2	404		1 88	17.6		Symptoms 16 yrs. Stationary.
23	I		1921	Lumbar	170	0	0		34	.	−	0122210000	0.080	28 1	672	0	2 30			−		20 2	463		1 91	14.2		Symptoms 16 yrs. Stationary.
24	I		1921	Lumbar		0	0		28	0	−	5310000000	0.061	18 2	662	0												Symptoms 2 yrs. Progressive
25	I		1921	Lumbar		0	0		42	0	−	0000000000	0.088	17.0	746	0		14 2	tr.	−	0.080	23 9	622	0		15 1	2.2	Symptoms 25+ yrs. Stationary.
26	I		1921	Lumbar		0	0		42	0	−	0000000000	0.069	16.9	685	0					0 101	26 2	486	0		14 −	1 4	Symptoms 25 + yrs. Stationary.
27	I		1921	Lumbar		4	0		57	0	−	0000000000												0				Symptoms 4 yrs. Progressive
28	F		1921	Lumbar		4	0		50	0	−	5554310000	0.061	*	681	0		0	tr.	−						17.6	2 6	Symptoms many yrs. Stationary.
29	F		1921	Lumbar		2	0		50	0	−	0000000000	0.077	26 3	703	0				−	0 102	26 3	505	0			. .	Symptoms 2 yrs. Mod. progressive.
30	M		1915	Lumbar	200		0			0	−	0034311000								−								Symptoms 6 yrs. Stationary.
31	M		1915	Lumbar	120	5	+			+	−	0000000000								−								Symptoms 8 yrs. Mod. progressive.
32			1916	Lumbar		0	sl. +	sl. +		0	−	0000000000								−								Symptoms 8 mos. Progressive.
33	F		1916	Lumbar		14	sl. +			sl. +	−	4445321000																Not progressive
34			1916	Lumbar	65	5	+			+		. . . . .								−								Symptoms 3 yrs. Stationary.
35	I		1916	Lumbar		0	0				−	0000000000								−								Symptoms 11 yrs. Stationary.
36	I		1916	Lumbar	150	3	0				−	.								−								Symptoms 17 yrs. Mod. progressive.
37	I		1921	Cistern		0	0		25	sl. +	.																	
38				Lumbar	130	0	0		30	sl. +	−	"paretic zone"																Symptoms 3 yrs. Mod. progressive.
39	M			Lumbar	140	7	0			.	−	"negative"																Recently progressive.
40				Lumbar	190	4	+			0	−																	Improving.
41				Lumbar	140	6	+		44	+	−																	Symptoms 9 yrs. Stationary.
42	M	22		Lumbar	180	1	0			. .	−									−								Symptoms 1 yr. Progressive.
43	F			Lumbar	200	12	+			+	−	1232100000								−								Symptoms 4 yrs. Paraplegia recently.
44			Apr., 1919	Lumbar		19	+	+		+	anti-comp.	. .																
45				Lumbar		24	+	+		+	−																	
46			July, 1919	Lumbar		42	+	+		0										−								Symptoms 9 mos. Progressive.
47	M	26	1916	Lumbar	80	10	0				−	0015554200								−								Symptoms 9 yrs. Stationary.
48	I	3	1916	Lumbar		0	0	0		0	−	. . .								−								Symptoms 18 yrs. Stationary.
49	M	3	1914	Lumbar		8					−	0000000000								−	0 133							Symptoms 7 mos. Rapidly progressive paraplegia. Laminectomy for cord tumor.
50	I	32	Dec., 1916	Lumbar		3	0	0		0	−	0012322100																Necropsy showed multiple sclerosis.
51			Dec., 1915	Lumbar						.	.	5555553200								−								Symptoms 4 yrs. Progressive
52	I	30	1920	Lumbar		2	+	+		0	−	1112210000								−								Symptoms 3 yrs. Progressive.
53	M	4	1920	Lumbar		3	0	0		0	−	. . . .								−								Stationary.
54	F	34	1916	Lumbar	40	8	0				−	4001100000								−								
55		35	1920	Lumbar	80	0	0			0	−	1110000000								−								

(Concluded on p. 119)

* Too low to read.

by the large number of paretic types obtained in the progressive cases, and by the fact that only 3 are entirely negative. Conversely it is seen that the stationary cases yield predominantly negative reactions.

In spite of the obvious inaccuracies in such a clinical and laboratory correlation, there is unquestionably some parallel between activity of the disease and pathological findings in the fluid. While it will be seen that the laboratory evidence of activity of the process rests upon a consideration of all tests; evaluation of these several tests shows that increase in cells and protein are less constant than the change in character of the goldsol curve.

Analysis of spinal fluid findings in patients examined more than once is of interest. Eight patients have been thus investigated. In all no great variation in tests is noted at different times with the exception of the gold reaction. In cases XII and XXXVIII this test remained essentially the same, in the former over a period of seven months, in the latter over a period of four years. The most significant changes (See Table II) are seen in Cases XI and XXXV, in both of which the character of the goldsol reaction changed materially, in the latter case during an interval of less than one month. In seeming contradiction to the conclusions reached above, there was no obvious change in the clinical course of the disease correlative with the change in these tests. It would be of considerable interest to determine in a larger series whether spinal fluid examinations are often as variable in an individual case as is indicated in these 2 patients.

Three patients, presenting symptoms suggestive of spinal cord tumor, were examined by means of combined cistern-lumbar puncture. A comparison of the fluids obtained from these two loci at the same time is of interest in that no distinctive difference is seen; this suggests that in these cases the pathological process is cerebral as well as spinal. The slightly greater protein content of the lumbar fluid is also seen in examination of normal individuals.

Concerning our chemical examinations other than the routine tests already discussed, we cannot be dogmatic. These studies were made as a matter of research, with the

hope of obtaining insight into this disease from possible metabolic disturbances which might show in the blood and spinal fluid. For example, it was possible that with the breaking down of myelin sheaths there might be thrown into the blood or fluid certain products of fat metabolism; yet we were unable to detect in either any trace of acetone bodies. Although the normal values of the various substances tested for in the fluid are not as yet certain, from the few reports in the literature and from our own work we must regard the figures obtained in multiple sclerosis as probably within normal limits. Compared with the figures in normal blood we also find no radical departure in this disease.

Conclusions. The spinal fluid findings in 38 cases of multiple sclerosis are given (See Table II).

There is no single fluid test of paramount value in the diagnosis of multiple sclerosis. However, correlation of all tests ordinarily performed on the spinal fluid indicates that it is seldom entirely normal, and that in 50 per cent of the cases of this series findings unusual in other diseases were obtained. This group of findings which we consider important is as follows: Fluid of normal appearance, obtained under normal or low pressure as registered by the manometer, showing a slight increase in cells (lymphocytes and arachnoid mononuclears), total protein normal or only slightly increased, globulin—a slight trace or absent, and a "paretic" goldsol curve with a negative Wassermann.

Correlation with the clinical picture suggests that this type of fluid indicates a progressive stage of multiple sclerosis. Conversely, normal or nearly normal fluids were found primarily in patients in whom no clinical progress had been recently apparent.

Certain chemical studies designed to show disorders of metabolism in this disease, performed upon blood and fluid, were within the limits of normal.

The following questions submitted to Dr. Ayer before the Commission, together with the answers to them, are here reported verbatim.

Dr. Patrick: I would like to ask whether the 1 case with forty cells was a progressive or a stationary case?

Dr. Ayer: That was a paraplegic case and was moderately active. That patient had had previous taps, three within one year, nineteen cells, twenty-four cells and forty-two.

Dr. Sachs: I would like to ask whether Dr. Ayer interpreted that goldsol reaction as indicative of an actual specific involvement; in other words, what view he took of it?

Dr. Ayer: It is not indicative. In talking with chemists and others, I cannot make out what the goldsol reaction is. I think perhaps the general feeling is that it is a specific protein test, but as to it meaning syphilis, I am perfectly satisfied that it does not. I see no reason for calling it the paretic goldsol reaction. That is simply the name that has been attached to it. I do not know any chemistry at all, but if this is a specific protein test, it is a little unusual, it seems to me, that we get practically normal total protein estimations in these fluids, some of them definitely normal, and yet in those cases we will get a paretic goldsol reaction. That is a little point that I am raising in my own mind, as to the cause of the colloidal gold reaction.

Dr. Timme: Dr. Leiner would like to know whether the presence of cholin was investigated in the fluid in view of the demyelination in this disease?

Dr. Ayer: I did not see any reports of cholin investigations and I made none myself.

Bacteriological Investigation of Multiple Sclerosis

Oscar Teague, M. D.

Dr. Tilney presented the results of Dr. Teague's investigations obtained during the past year.

I believe this work has been the most extensive and most comprehensive piece of investigation on this subject so far accomplished. The work is to be continued for a considerable period in the laboratory for experimental neurology at the College of Physicians and Surgeons; and the results of further investigations and the completion of the present series will be reported to the Association in subsequent communications.

In all, there are 7 main prior investigations that have been carried on, all falling within the period of the last eight years, and I will give you a very brief synopsis of the results of this bacteriological investigation.

The first was in 1913, by Bullock, now Gye, whose method of procedure was the injection of spinal fluid, filtered and

unfiltered, into a number of rabbits and 1 cat. This injected material, the spinal fluid, was obtained from a rapidly progressive case of multiple sclerosis. As a result of his investigations, several rabbits became paralyzed and he concluded that multiple sclerosis was a disease due to a filter passing organism, or to a water soluble poison.

In 1917 Kuhn and Steiner employed methods of injection, using spinal fluid, spinal fluid mixed with blood, and blood from patients suffering from multiple sclerosis. They employed guinea-pigs and rabbits and were able to pass a paralytic disease through four passages in guinea-pigs and two passages in rabbits. They came to the conclusion that the disease was due to a spirochete, which was found in the blood of the paralyzed rabbits and guinea-pigs, and that this spirochete was like the leptospira of Weil's disease—infectious jaundice. They believe this organism is the essential agent in the disease.

In 1918 two investigators, Simons and Marinesco, confirmed the findings of Gye and Kuhn and Steiner. Their investigation was rather more limited in the number of experimental animals and in patients employed.

In 1921 Rothfeld, Freund and Hornowski, using blood of patients suffering with multiple sclerosis, spinal fluid and organ emulsions, injected them into guinea-pigs and rabbits, found entirely negative results, through a series of a large number of experimental animals. Their bacteriological results were uniformly negative; they were unable to find the Kuhn and Steiner spirochete, though all the usual methods of search were made. Their animals died, many of them, from a coccidiosis, pulmonary inflammation, cellular infiltration of the kidney and tuberculosis.

A little later in 1921, Magnus in Christiania used injections of blood from 23 patients with multiple sclerosis, in 42 guinea-pigs and 7 rabbits. None of his animals developed paralysis or other sickness, except two, which died of a local infection in the brain, explained on the basis of a local process in the ear.

Gye, again in 1921, made a more extended control of his original investigation, using spinal fluid, brain emulsions of animals involved by the disease, which he injected intra-

muscularly, subcutaneously, and subdurally, using 15 guinea-pigs and 129 rabbits, from 21 selected cases of multiple sclerosis. All the guinea-pigs survived. One hundred and twelve of the rabbits survived; 17 of them became ill and paralyzed. Among those rabbits which died, he also observed an extensive coccidiosis; but he concludes that multiple sclerosis is probably an infectious disease, the virus of which may sometimes be found in the spinal fluid.

All in all, then, the previous work shows 5 investigators who have come to the conclusion that the disease is infectious, 2 of them that it is due to a specific spirochete, and 4, on the other hand, oppose this supposition on the ground of their own negative findings in experimental animals.

The present investigations concerning the bacteriology of multiple sclerosis were carried on under a grant from the Commonwealth Foundation, made to the New York Neurological Institute for this purpose. The experimental work was conducted by Dr. Teague. The experiments thus far have been confined to the following attempts:

1. To cultivate spirochetes or other organisions from the blood or spinal fluid of patients with multiple sclerosis.

2. To produce recognizable symptoms in animals by inoculating them with the blood or spinal fluid of patients suffering from multiple sclerosis.

3. To demonstrate spirochetes in the blood or organs of the inoculated animals by darkfield examination or by cultural methods.

The number of cases of multiple sclerosis employed was 16, divided as follows, with reference to the nature of the disease:

Group 1. Acute—rapidly developing and progressive cases	3
Group 2. Chronically progressive cases	5
Group 3. Stationary cases of long standing	8.

The animals employed were guinea-pigs, rabbits, rats, mice, cats, dogs and monkeys. The average number of animals used in each case was 14. The total number of animals used in all of the experiments was 220.

The method of inoculation: In guinea-pigs the inoculation was in all cases intraperitoneal. A few injections were made into the globe of the eye; the amount 1 c. c. of spinal fluid or 2 c. c. of blood diluted one-third.

Rabbits were inoculated intraperitoneally, 2 c. c. of spinal fluid or 2 c. c. of blood one-third diluted, into the eyeball. The injection into the eye was made by passing a needle into the vitreous and aspirating about ½ c. c. of the vitreous; the needle being left in place, the syringe removed and replaced by one containing spinal fluid or blood, when pressure was exerted on the plunger until some resistance was met with. A few of the rabbits were inoculated directly into the brain substance, a small piece of bone having been removed from the skull from five to ten days previously.

The rats were inoculated intraperitoneally.
The mice were inoculated intraperitoneally.
The cats were inoculated into the vitreous of the eye.
The dog was inoculated into the vitreous of the eye.
The monkeys were inoculated intraperitoneally.

From the first 5 patients the animals were given mixtures of spinal fluid and blood, but from all other cases each animal received either spinal fluid or blood alone.

Results. A number of the guinea-pigs and mice have died of lobar pneumonia, smears of the lungs showing Gram-positive cocci, which were presumably pneumococci.

Some of the rabbits have gradually grown thinner and weaker without showing definite paralysis of any of the extremities. Some of these have had a purulent discharge from the nostrils and showed small Gram-negative bacilli in the blood at death. Others had coccidial nodules in the liver or coccidial cysts in the omentum and the cause of death was ascribed to coccidiosis.

In a few of the animals no cause of death was determined.

It is worth noting that not a single one of the inoculated rats has died. The rats come of healthy stock bred in the laboratory.

The monkeys, dogs and cats have remained entirely well.

None of the cultures of the spinal fluid or blood of patients, nor of the blood or tissues of the inoculated animals have shown spirochetes.

The vitreous of the inoculated eye aspirated at varying intervals, after inoculation from some of the rabbits, has shown no spirochetes.

From this investigation, up to the present day, we have practically negative results. This investigation does not confirm the work of Gye nor that of Kuhn and Steiner, nor Simons nor Marinesco, and it is presented simply because of the large amount of material which has been used in its prosecution and also because of the fact that it has this negative return up to the present.

The following questions submitted to Dr. Tilney before the Commission, together with the answers to them, are here reported verbatim.

Dr. Taylor: I should like to ask Dr. Tilney what is projected to complete this investigation?

Dr. Tilney: The selection of additional cases that perhaps are more favorable in their symptomatology, more calculated to be in the group in which the other investigators have found their positive results.

Dr. Meyer: Are there any provisions to get material from operations or from fresh autopsies?

Dr. Tilney: Yes, there are such provisions; there are several cases now that are awaiting operation, from which we expect to get the spinal fluid, the autopsy arrangement being, of course, dependent entirely upon circumstance.

Dr. Jelliffe: Are paralyses in rabbits of any real use as argumentative material? That is the first question. Second: Are not rabbits prone to paralytic attacks from a great host of infections?

Dr. Tilney: I think the answer to the second question covers the first: Rabbits are prone to paralysis from a great many other causes and the mere fact that an experimental animal develops a paralysis is absolutely no indication that the cause is multiple sclerosis or anything allied to it. The only test that could settle that question is the pathology of the central nervous system; and if the pathology discovered there corresponds to the known processes of multiple sclerosis, then of course the answer is furnished; otherwise, the clinical appearance of paralysis is no answer to the question at all.

The Conclusions of the Commission

Symptom Composites Indicative of Multiple Sclerosis. The evidence submitted to the Commission on the basis of the clinical studies of multiple sclerosis emphasizes again the polymorphous character of the symptoms of this disease.

It is the opinion of the Commission that the several neuron systems of the neuraxis may be involved separately or in numerous combinations in such a way as to produce a great variety and often a kaleidoscopic display of symptoms. No one particular group of symptoms, however, may be held to be essential to the diagnosis. On the other hand, any combination of symptoms indicative of a multiplicity of central lesions, not attributable to some infection or injury, warrants the diagnosis of multiple sclerosis.

Triad of Charcot. Charcot's triad of symptoms noted by early observers, namely, nystagmus, intention tremor and scanning speech, should not be held as a symptomatic combination necessary to the diagnosis of multiple sclerosis. Earlier concepts of the disease were based on fully developed chronic cases in which the well-known triad above mentioned, was almost invariably present. This triad does not appear in many cases in the initial stages of the disease, and is often absent during its entire course.

Frequency and Incidence. It is the opinion of the Commission that multiple sclerosis is by no means so infrequent in this country as has been held by many authorities. There seem to be good reasons for believing that it is among the most common of organic diseases affecting the nervous system. The disease manifests itself most commonly between the twentieth and fortieth years. It may, however, make its first appearance as early as the second decade or as late as the sixth.

Onset and Course. The Commission believes it has been established that the onset of the disease, like its symptoms, may be variable. As a rule, the clinical manifestations make their appearance insidiously. In certain instances, however, the onset may occur as an acute fulmination with the development of symptoms at their maximum intensity.

A conspicuous tendency for the disease to develop transitory repeated and brief palsies in the somatic musculature, prior to the establishment of a definite multiple sclerosis symptom complex, is clearly defined by the observations of Drs. Cadwalader and McConnell.

In the opinion of the Commission, many of the symptoms in the early stages of multiple sclerosis are so slight as to escape detection, and so transitory as to make little impression on the recollection of the patient. These symptoms, however, after subsiding without leaving a trace, may occur later and progressively evolve into a fully developed clinical picture of the disease. Remissions of this kind, at the onset, are believed to be common and probably occur in the majority of cases.

To the early, fleeting disturbances which may usher in the disease, such as impairment of vision, ocular paralyses, weakness of one or more of the extremities, with or without paresthesia, the Commission wishes to call especial attention from the viewpoint of diagnosis and prognosis.

Remissions during the course of the disease, even after the development of pronounced symptoms, are also of frequent occurrence and of much diagnostic significance. Such remissions are at times sufficiently misleading to arouse the suspicion that the patient is suffering from hysteria or some functional form of nervous disease.

Motor Symptoms. The disease usually manifests itself as weakness or stiffness in one or both lower extremities, gradually or intermittently culminating in a spastic paralysis. It is the opinion of the Commission that the spastic paralysis most frequently involves both legs. On the other hand, the motor disorder may manifest itself in the form of bulbar, cerebellar or hemiplegic disturbances. The type of motor defect in the vast majority of cases results from upper motor neuron involvement. In not a few instances, however, paralysis of the lower motor neuron variety has been observed, due to the extension of the plaque into the ventral gray columns of the cord. In distribution the paralyses may be monoplegic, hemiplegic, hemiparaplegic or tetraplegic.

Increase in the deep reflexes appears, from Dr. Sachs' tabulation, to be the most constant physical finding in a large

group of cases, hyperreflexia being present in 90 per cent. The Commission agrees with Dr. Sachs in the importance which he has attached to the loss of the abdominal reflexes. This sign was present in 83.7 per cent of the patients observed by him. The tabulation of the signs and symptoms of multiple sclerosis in the order of their diagnostic importance, formulated by Dr. Sachs and appearing on page 50 represents in the opinion of the Commission a most illuminating survey of the symptomatology.

General Somatic Sensory Symptoms. These symptoms occur in something more than one-half of the cases. They are usually patchy in distribution, but objectively may be of the type referable to posterior column disturbance; or again, they may produce defects in algesic and thermic sensibility. Subjectively, the sensory disturbances may manifest themselves as numbness, tingling, pain and any of the other various types of dysesthesia. In general, the objective and subjective sensory changes are vague, irregular and variable.

Cranial Nerve Disorders. Nystagmus, with or without ocular palsies and diplopia, constitutes the most frequent motor disturbance in the sphere of cranial nerve innervation; while temporal pallor of the optic disc with scotomata has a very high representation in cranial nerve disturbances.

The Commission agrees with Dr. Friesner's contention that nystagmus must depend upon some lesion in the mechanism associating the vestibular with the oculomotor apparatus; it is believed, however, that there is not sufficient anatomical evidence to identify the exact location of such a lesion, nor to explain the mechanism of nystagmus, past-pointing, vertigo and the falling reactions. The importance of nystagmus as a symptom in the diagnosis of multiple sclerosis, however, stands unassailed.

The evidence submitted by Dr. Holden concerning the ocular manifestations of multiple sclerosis, convinces the Commission that the most frequent disorders in the territory of the oculo-visual innervation are nystagmus scotomata and temporal pallor of the optic discs. The presence of temporal pallor without marked visual reduction, and conversely the presence a large scotomata without apparent demonstrable

change in the nerve head, is of much diagnostic importance. Temporal pallor is one of the most valuable diagnostic signs in multiple sclerosis, since it is found in practically no other nervous disease. The rarity of blindness, emphasized by Dr. Holden, and also the relative infrequency of swelling of the discs, are diagnostic features of value in the differential diagnosis. The blurring of the disc edges, together with a slight reddening during acute periods of the disease, merits attention, and the occurrence of numerous small scotomata especially with other signs of multiple sclerosis, has an important bearing on the diagnosis.

The Commission feels convinced that Dr. Holden's scepticism with reference to the concentric contraction of the visual fields, is well founded, and would place much diagnostic emphasis on the lacunar losses of visual acuity, particularly in central and circumcentral scotomata.

The fluctuating and transitory character of the ocular and optic changes is in consonance with the varying intensity of other symptomatic features of the disease.

The facial, hypoglossal and glossopharyngeal nerves appear to be less frequently involved, than the optic and ocular nerves but must be regarded as among the cranial nerves showing a definite proclivity to impairment by the pathological process. The defects in the cranial nerve innervations are most commonly nuclear, but may be in the internuclear or supernuclear connections.

Mental Symptoms. It is the conclusion of the Commission that there is no particular psychic disorder characteristic of this disease. The formation of patches in the brain does not lead to the development of any of the well recognized forms of psychosis. The euphoria, mentioned by Drs. Brown and Davis, may be associated with the disease, but is not as characteristic a feature here as, for example, in general paresis. The absence of mental deterioration, even where well defined pathological changes are recognizable in the cerebral hemisphere, seems to emphasize the ability of the central nervous system to adjust itself to or even withstand serious disorganizing influences.

The occurrence of hallucinations of sight or hearing, together with the development of definite trends in multiple

sclerosis, may be duplicated in a group of cases suffering from other chronic degenerative changes, as for example, in diseases of the respiratory, circulatory and other systems of the general organization.

The probability that certain action patterns resulting from unconscious psychological repressions and determining certain disturbances in the vascular distribution which result in the plaque formation of multiple sclerosis, was discussed and emphasized by Dr. Jelliffe. At present the Commission feels that it must accept this proposal merely as a suggestion which, in the absence of confirmatory observations and further proof, has not yet been established on a sufficiently firm basis to determine its validity.

Involvement of the Sympathetic System and the Endocrines. Based upon the work of Drs. Pardee and Kraus, the Commission concludes that the sympathetic nervous system and the glands of internal secretion manifest no definite evidence of involvement which may be directly traceable to multiple sclerosis. This immunity seems to be due to the automaticity which the segmental mechanism of the spinal cord is capable of assuming in relation to the visceral functions when cut off from higher influences. Disturbances in the control of the bladder and rectum frequently occur in this disease, although little is known of the exact mechanism disturbed by the pathological process. The Commission concludes that there is no valid evidence at present showing a disturbance in the ductless glands and believes that such cases as occur are due to coincident complications.

Serology and Bacteriology. It is the opinion of the Commission based on the studies of the cerebrospinal fluid and blood in multiple sclerosis by Drs. J. B. Ayer and H. B. Foster, that there is no deviation from the normal hemal composition traceable to this disease and nothing pathognomonic of the process of multiple sclerosis to be determined by an examination of the spinal fluid. The fluid is clear, colorless; its pressure tends to be low rather than high, and there is no marked pleocytosis, the highest cell count being 42 and the protein content usually about normal. The Wassermann reaction is uniformly negative. In 50 per cent of cases a paretic type of colloidal gold curve was

present; about 16 per cent showed the luetic type of curve; about 7 per cent showed variable curves; and in about 27 per cent the curve was negative. Pleocytosis was found to be present only in actively advancing cases, but this same reaction is often absent in cases which are clinically progressive. Marked changes in the character of the disease are not necessarily reflected by concomitant changes in the character of the spinal fluid. The Commission concludes, therefore, that the spinal fluid, while it may not be normal, contains nothing pathognomonic of multiple sclerosis. The abnormal colloidal gold curves, occasional pleocytosis, fluctuations in the protein content, are all deviations from the normal; yet none of these is constantly present and none is in any way to be regarded as diagnostic of the disease.

In considering the results of the investigations carried on by Dr. Oscar Teague in the effort to isolate the active etiological factor producing multiple sclerosis, as reported by Dr. Frederick Tilney, the Commission concludes that at present there is no incontrovertible evidence that the causative factor has been isolated. Failure of corroborative experiments and the inconsistencies of reported findings, leave the etiological factor almost completely in the dark. The investigations reported by Dr. Tilney and carried on by Dr. Teague are negative in all respects, although not as yet checked by post-mortem examination. Further development of this problem is to be carried on during the ensuing years.

CHAPTER III

The Differential Diagnosis, Course and Treatment of Multiple Sclerosis

Bernard Sachs, M. D., and Emanuel D. Friedman, M. D.

The section covering the differential diagnosis, the course and treatment of multiple sclerosis was prepared by Dr. Emanuel D. Friedman of New York City and submitted to the Commission of the Association. This contribution was not presented before the meeting of the Association held in December, 1921, at New York City.

The differential diagnosis between syphilis and multiple sclerosis is described by Dr. Bernard Sachs of New York City.

Before discussing the differential diagnosis of multiple sclerosis, we would call attention once more to certain points in diagnosis worthy of emphasis.

If the Charcot triad (intention tremor, scanning speech and nystagmus) be present, the diagnosis is relatively simple. But this combination of symptoms is found only in a small proportion of cases, and then only when the disease is fully developed. The diagnosis is particularly difficult in cases without multiple foci which have an apoplectiform onset. It is important in every case of acutely developing focal disease of the brain and spinal cord in a previously healthy young individual, to think of multiple sclerosis if lues can be excluded. Because of the widespread dissemination of the lesions in multiple sclerosis, there is scarcely a syndrome which does not occur in this disease. Hemiplegias developing over night, aphasias, unilateral sensory disturbances, myelitides with acute Brown-Séquard syndromes, signs pointing to involvment of the lowermost cord (sacral type of Oppenheim and Mendel) and especially acute amaurosis, all may be encountered in disseminated sclerosis. Often after several weeks all subjective signs disappear. This

rapid change in the clinical picture is of considerable diagnostic importance. After several months or years, new symptoms appear. These may again be transitory, but more or less permanent disability remains.

There is a type which differs from this acute relapsing form. In the former, the disease process is more continuous. It manifests itself in ready fatigue, general nervousness and the advent of any of the signs enumerated in our table given under the general symptomatology of the disease. Between these two types, there are all kinds of transitional forms. The clinical signs point to a widespread anatomic process and to a multiplicity of foci. Remissions and exacerbation of symptoms are characteristic of the disease.

DIFFERENTIAL DIAGNOSIS

Because of the disseminated lesions, multiple sclerosis may simulate many forms of organic, or functional disease. It may suggest tabes, although the pupillary phenomena and the serologic evidences of lues are wanting. Marburg and others have stressed in this connection a discrepancy in the character of the reflexes. For example, diminished knee-jerks associated with active ankle-jerks or a positive Babinski sign, are considered suggestive of multiple sclerosis and are due to a plaque in the pathway of the reflex arc of the quadriceps extensor muscle.

Multiple sclerosis often appears in the guise of a spastic paraplegia and only after a period of years, and with the development of eye signs, can the diagnosis be established. This often proves to be the case also for those types of multiple sclerosis which resemble *amyotrophic lateral sclerosis.* In multiple sclerosis the absence of a steady progression in the symptoms is of great importance.

Acute inflammatory diseases of the nervous system (encephalitis or encephalomyelitis) can be differentiated from multiple sclerosis by the presence of fever, the more rapid course, its incidence following acute infectious disease, the greater tendency toward a fatal issue, the absence of remissions and the evidences of greater and more diffuse invasion of the spinal cord substance. The sequelae of these acute

myelitides show no tendency to progression. This differential diagnosis is not altogether simple, since acute types of multiple sclerosis do occur. The indefinite character of the sensory changes, the absence of distinct muscular atrophy, vasomotor or trophic disturbances will favor the diagnosis of multiple sclerosis.

Syringomyelia is usually easily differentiated from multiple sclerosis although the typical dissociated sensory disturbance has been observed in both diseases.

Cerebral neoplasm is another of the diseases from which multiple sclerosis must be distinguished, particularly since headache, vertigo and vomiting may occur at the onset of multiple sclerosis and may be associated with changes in the optic discs. Other symptoms of intracranial pressure, however, are usually not marked. The disc changes, if present, resemble optic neuritis rather than choked disc; these changes are often unilateral. Both Bruns and Nonne have observed cases in which the differential diagnosis was extremely difficult. This is particularly so in the cases associated with hydrocephalus. The long interval elapsing between the onset of disturbances of vision and of other signs of disease is in favor of multiple sclerosis. Westphal, Maloney, Brissaud and Marburg have reported such cases. Multiple sclerosis is particularly apt to be confounded with a cerebello-pontine angle tumor. Frequent recession of the symptoms and the subsequent course with the development of new symptoms indicating other foci, will serve to differentiate between the two conditions.

Nonne also described types of multiple sclerosis resembling *spinal cord neoplasm.* In these cases also, the further course of the disease, with the absence of steady progression and the possible remission of symptoms, favors multiple sclerosis with pseudo-tumor signs (meningitis serosa circumscripta). In multiple sclerosis there can usually be demonstrated the existence of some other focus besides the one producing a level lesion in the cord. This also holds true for the cases of *chronic internal hydrocephalus* which may simulate multiple sclerosis.

The Déjérine-Thomas type of *cerebellar atrophy* can be differentiated from multiple sclerosis by the absence of

the cardinal signs of the latter disease or the presence of spastic phenomena in the lower extremities. Mingazzini emphasizes the absence of epilepsy and imbecility in multiple sclerosis which are common in cases of cerebellar atrophy and point to cerebral agenesis.

Pseudosclerosis may resemble multiple sclerosis very closely. In both diseases there may be paralysis, pain, paresthesia, attacks of unconsciousness and disturbances in mentality. The more pronounced types of dementia are characteristic of pseudosclerosis; disturbances of speech are common to both. In multiple sclerosis, tremors are more frequent than contractures or spasms, as are also sensory disturbances and loss of the superficial reflexes. Epileptic seizures are present in about 50 per cent of the cases of pseudosclerosis. They are much rarer in multiple sclerosis. Nystagmus and abnormal disc findings are rare in pseudosclerosis. The tremor of pseudosclerosis is very coarse. In pseudosclerosis the speech is rather dysarthric.*

Since multiple sclerosis occurs in childhood, one must also differentiate the disease from *tuberous sclerosis* (Neurath, A. Vogt) and from *aplasia axialis extracorticalis congenita* (Pelizaeus-Merzbacher). The former is characterized by idiocy, imbecility and epilepsy. The latter has much in common with multiple sclerosis (nystagmus, intention tremor and absence of superficial reflexes). It begins however in the first years of life, progresses very rapidly, is associated with trophic changes in the bones and the lower extremities, and is frequently familial.

Multiple areas of softening as a result of disease of the arteries may lead to a syndrome resembling multiple sclerosis (spasticity, tremor and disturbances in gait). The disturbances in locomotion, however, of multiple sclerosis are quite different from the characteristic senile gait. The age of the patient, and other evidences of sclerosis will be the deciding factors in such cases.

* Oppenheim characterizes pseudosclerosis in the following terms. It begins in childhood; dementia occurs early, there is coarse tremor and dysarthria. Muscular spasms are common; nystagmus, disc changes or true spastic phenomena are not observed. The pathological basis of this disease is a mild sclerosis of the brain with peculiar changes in the glia of the basal ganglia.

There is one differential diagnosis of paramount importance, and to that it will be well to give full consideration. In a given case, is the patient suffering from multiple sclerosis, or from *multiple cerebrospinal syphilis*? In both diseases we are confronted with patients who have in the course of a few months or possibly a few years developed from very slight beginnings a more or less marked spastic weakness of the lower extremities associated with an increase in all the deep reflexes. In both diseases, there are very marked periods of remission and of exacerbation. The remissions are just as marked in the one as in the other disease.

In the cases of cerebrospinal lues, there are pupillary symptoms and ocular palsies that point indubitably to the constitutional infection, and there are in the majority of instances the positive biologic findings, the positive Wassermann reaction in the blood, the positive reaction in the spinal fluid with the increase in globulin and a pleocytosis.

In the cases of disseminated sclerosis, there are very pronounced nystagmus, transitory ocular pareses, more or less marked intention tremor, as well as spastic contracture of the limbs.

To be sure, there are also cases of cerebrospinal lues in which a nystagmus occurs and in which there may be a slight ataxia or ataxic tremor of the upper extremities.

If there is very distinct syllabic speech or scanning speech, the diagnosis of disseminated sclerosis is ready to hand.

But the trouble is that there are also some cases of cerebrospinal lues in which there may be a more or less marked dysarthria, bulbar or cerebellar in types. The two groups approach each other so closely that in not a few instances it is well-nigh impossible to state definitely from which one of the two diseases the patient is suffering. Catola, Spiller, Sachs and others have emphasized the marked similarity in the clinical syndrome. But there are a few differential signs of great importance.

First and foremost, in disseminated sclerosis the pupillary reactions are almost universally normal, whereas in fully 90 per cent of cases of cerebrospinal lues the immobility of the pupils is a very early and very constant symptom. If there is an irregular contour of the pupils as well, the

suspicion of luetic disease is fully corroborated. The ocular palsies in lues are early and complete; in multiple sclerosis they are partial and transitory.

Moreover, in disseminated sclerosis the serological findings are practically negative; whereas in cerebrospinal lues the findings are as a rule positive enough to confirm the diagnosis of lues.

There is one other condition to which we attach great significance, namely, that the spasticity in cerebrospinal lues is greater than that found in the cases of disseminated sclerosis, unless the patients are in or near the terminal stage. In the early stages of disseminated sclerosis, there is weakness and only a very slight degree of spasticity. In cerebrospinal lues, there is marked spasticity and relatively less weakness.

As Erb pointed out years ago, the rigidity of the spinal syphilitic is excessive. He would get about easily if there were not inordinate spasticity of gait. The average patient suffering from multiple sclerosis has in the first years of his illness a weakness which becomes more and more pronounced, but the spasticity is far less marked than is the paresis. Even so, there are further difficulties to be considered. May not disseminated sclerosis occur in a person suffering from constitutional lues, who may present immobile pupils and slightly positive serological findings? But if he have a number of the other important symptoms of disseminated sclerosis, are we not justified in diagnosing multiple sclerosis in a person suffering from constitutional lues rather than in diagnosing cerebrospinal lues pure and simple? The serologic tests,* the pupillary findings and the greater tendency to spasticity in lues spinalis are diagnostic points to be considered. The response to treatment may in some cases point to the luetic origin of the symptoms. A coexisting luetic chorioretinitis will also be of service in this connection.

Let us emphasize these differences by insisting that excessive spasticity or spasticity far greater than the paresis,

* Spinal fluid was found negative in 114 out of 122 cases studied. The spinal Wassermann test was negative in all these cases. In 8 cases the cell count was above normal, the figures being 12, 13, 16, 16, 20, 30, 30 and 40 cells respectively. In 3 cases, the globulin was increased.

argues in favor of the luetic infection. Immobility of the pupils and positive biologic findings help to corroborate this diagnosis. Slight spasticity, normal pupillary reactions, negative findings and the presence of other very positive signs, will lead to the diagnosis of disseminated sclerosis.

To illustrate the difficulties of the diagnosis, let us present briefly the symptoms of 2 cases.

The first patient is a man, now thirty-nine years of age, who has been under observation two years and three months. At the first examination his chief complaint was a feeling of weakness in the knees as well as in the right foot when walking. He has been married sixteen years and has four healthy children. He gave the history of a papilloma of the left vocal cord having been removed eight months before his first visit. He had a chronic nasopharyngitis. He brought evidence to show that lumbar puncture had been done and the findings were negative. The Wassermann in the blood and the spinal fluid was negative. He had a slightly spastic gait; all the deep reflexes were exaggerated; there was a very slight suspicion of speech disturbance, although the patient himself claimed that his speech was normal.

During the time that he was under observation there was very distinct improvement under treatment by cacodylate injections. There was no intention tremor. He had perfect control over his vesical and rectal reflexes. His pupils reacted well; there was a very slight nystagmus. During the year 1920 the spasticity was very much lessened, but beginning with the spring of 1921 there was a marked return of weakness of the legs and the spasticity has become extreme, so that at the present time he has great difficulty in mounting stairs or in getting into an automobile; but his pupils are entirely normal, the Wassermann reaction of the blood remains negative, the abdominal reflexes are lively, there is no marked disturbance of speech, there is very little intention tremor, and there is very slight nystagmus.

We have been inclined to regard this patient as suffering from disseminated sclerosis, but the presence of the abdominal reflexes and the inordinate spasticity leave a doubt in our minds as to whether or not the case may, after all, be one of cerebrospinal lues, in spite of the normal pupils and the negative serological findings.

Were Marie to see this patient, we have no doubt he would feel justified in claiming that he was suffering from cerebro-

spinal lues and not from multiple sclerosis. There is some comfort in knowing that there are relatively few cases that present as marked difficulties as does this patient.

In the second case the symptoms are briefly as follows:

A clerk, aged thirty-eight, born in the United States, admitted January 30, 1918, gave the history of having had a fall eleven years previous, and that since this accident he was unable to get about. The records show that there was a weakness and trembling of the legs, urgency of urination, marked exaggeration of all the deep reflexes, including double Babinski, that the abdominal reflexes were feebler on the right side, the cremasteric reflexes were absent, and speech hesitant; that the patient had had a number of convulsions, the first seizure at the age of twenty-two. At a subsequent examination (February 15th) it was stated that the head was tilted to the left, that there was temporal pallor of the discs, that the lumbar puncture fluid was negative, that there was disturbance of sensation in the toes, and that the retina showed a picture of luetic degeneration; that the right pupil was larger than the left, that it reacted sluggishly; that there was lateral nystagmus, weakness of the left face, weakness of the right grip; loss of muscle sensation in the upper extremities, head tremor, ataxia, and tremor in both hands; moreover, that there were uncontrollable laughter and double Babinski, and that all the abdominal reflexes were absent, except the left upper. Again, the Wassermann reaction was found negative in the blood and in the spinal fluid.

Death was sudden. The post-mortem examination in this case revealed a primary idiopathic internal hydrocephalus, multiple sclerosis, pachymeningitis. There were thickening of the pia-arachnoid and marked enlargement of the ventricles. The ependyma was thickened. The spinal cord was markedly diminished in circumference and showed degeneration of the dorsal tracts and crossed pyramidal tracts on the right side.

Clinically, this patient presented the symptoms of multiple sclerosis with a suspicion of constitutional lues; and we would interpret the report of the pathologist in the same way—a combination of sclerotic plaques and a chronic luetic process.

The mental changes in multiple sclerosis are occasionally marked enough to suggest the development of general paresis. In such cases the Wassermann reaction in the blood and spinal fluid, the tremor about the mouth and tongue,

the more marked dementia and the delusions of grandeur will favor the diagnosis of general paresis. The tremor, too, of general paresis is not constant nor of the intention type. Speech is more slurring and tremulous, and the repetition of spoken words is distinctly difficult.

Paralysis agitans in rare instances shows a tremor somewhat like that of multiple sclerosis. Berger has found disturbances in gait resembling paralysis agitans in some of his cases of multiple sclerosis. The age of the patient, however, the mask-like facies and the absence of eye signs would be deciding factors.

Cases of essential tremor have been confused with multiple sclerosis. The presence of the abdominal reflexes, the absence of eye signs and the familial history will serve to decide the diagnosis.

Multiple sclerosis must be differentiated from *Friedreich's ataxia*. In this disease however, there is a distinct familial history, the abdominal reflexes are usually preserved, the deep reflexes are generally diminished and there are no fundus changes. The course of the disease shows a steady downward trend without remissions: also a typical scoliosis and deformity of the feet (*pes cavus*). *Marie's hereditary ataxia* must also be differentiated from types of multiple sclerosis with predominant cerebellar manifestations. The criteria spoken of in connection with Friedreich's ataxia will be of service.

Multiple sclerosis may begin as an acute apoplexy. In these cases, affecting usually young individuals, the absence of lues, endocarditis or hypertension, the marked improvement of the hemiplegic symptoms and the subsequent development of symptoms pointing to other foci, will serve to establish the correct diagnosis.

Epidemic encephalitis may resemble multiple sclerosis. In fact, Marie spoke of the former as acute multiple sclerosis. The present epidemic is still too recent to permit us to state definitely whether or not epidemic encephalitis may give rise to the tissue changes of multiple sclerosis. Pathological studies by Economo, Strauss and Globus, Schaller and Oliver in cases of subacute and protracted encephalitis in which they demonstrated persistent perivascular infiltration

with changes in the glia would seem to point to the possibility of such a development.

Subacute combined sclerosis of the cord may resemble multiple sclerosis, but the former develops later in life and the tendency is progressively downward. There are no fundus changes and the evidences of posterior column involvement are very marked. One can usually demonstrate in these cases some etiological factor such as pernicious anemia or cachexia from other causes. In some of these cases there is a peculiar glossy atrophic skin.

Finally, multiple sclerosis must be differentiated from *hysteria*. This is particularly true early in the disease when marked recession of symptoms may take place. One frequently finds these cases labeled hysterical amaurosis or functional dysbasia. The sensory symptoms are interpreted also as being functional, but a careful examination will reveal to the trained neurologist some definite evidences of organic disease of the nervous system. Changes in the discs, diminution of the abdominal reflexes, slight disturbances in sensation, a history of diplopia, mild urinary signs such as urgency or slight retention will serve as important deciding factors. Marburg believes that the hysteroid manifestations in multiple sclerosis may be the expression of organic changes in the brain.

In summarizing the clinical studies, let us again suggest that the diagnosis of disseminated sclerosis is warranted in the presence of a combination of any number of the important signs as enumerated in the table presented in a preceding chapter, and particularly if corroborated by the entirely negative character of the pupillary reactions and of the biological tests.

That there will be occasional pitfalls and errors may be conceded, but that is practically as true of disseminated sclerosis as it is of all other organic diseases of the central nervous system.

Course. Multiple sclerosis is usually a chronic disease with a tendency to progressive deterioration in spite of frequent remission of symptoms. In chronic cases, the symptoms gradually increase in number and severity. The average duration of the disease is from five to twenty years. Byrom

Bramwell reported a case lasting thirty-three years. Some observers have reported cases which ran their whole course in a period varying from several months to one year. Marburg maintains that the acute onset is often only apparent because the prodromal phenomena are frequently overlooked. The remissions of the disease may last months and sometimes years, but with each acute exacerbation the patient becomes more and more incapacitated. These acute exacerbations frequently come on spontaneously or may follow exposure to cold, exertion, trauma, some acute infectious disease or the puerperium. The causes of death in multiple sclerosis, unless there be bulbar involvement, are tuberculosis, terminal ascending infections of the kidney, sepsis from decubitus and pneumonia.

Complications. Multiple sclerosis is frequently found in association with hysteria. It has been found with tabes dorsalis by Westphal and Mills, with paralysis agitans by Oppenheim, Jolly and Sachs, with myxedema by Raymond and Guillain, with syringomyelia by Schulle. Oppenheim has also found it associated with idiopathic epilepsy.

Prognosis. The prognosis with regard to life is not unfavorable. The disease may last decades. In cases with involvement of the medulla oblongata, death may occur relatively early, although Oppenheim reports a case with recurring attacks of asphyxia, aphonia and signs of vagus paralysis, that lasted several years. There is very little tendency toward complete recovery, although Charcot and Marie have emphasized the possibility of the disease becoming arrested. It should be borne in mind that very often a remission of the disease, especially in the early cases, may simulate a full recovery.

Treatment. Physical exertion should be avoided. Extremes of temperature are also harmful. Faradic electricity should be avoided. It is particularly important not to confound the early cases of multiple sclerosis with hysteria and to treat them as such.

We have no specific remedies for this disease. Iodides according to some observers are of value. Colloidal silver preparations either by inunction or by intravenous injection have been recommended by Marburg and others. Nonne

recommends intramuscular injections of fibrolysin about every five to seven days. For the tremor, veronal and hyoscin have been advised. The greatest benefit apparently is obtained from arsenical treatment, given either by mouth or through injections of cacodylate of soda. Sodium nucleinate has also been advised. Treatment at various *spas* is sometimes helpful. Warm baths, moderate and skillful massage, and methodic exercises are in order.

In the acute attacks, eliminative treatment is of service. In severe cases with spastic contractures the Foerster operation has been recommended, although Foerster himself is not enthusiastic about this method of treatment. Constipation is sometimes extremely marked and this should be counteracted by means of enemata, cascara or other purgatives. For the incontinence of urine which at times is quite annoying, 5 to 8 minims of the tincture of belladonna should be administered two or three times a day. In cases with marked weakness of the legs, passive movements, massage and mild exercise frequently lead to definite improvement. For the spasticity, passive motion, warm baths and baking have proved beneficial. For the ataxia, Fraenkel exercises should be prescribed. All other methods of reeducation are also helpful.

The recent work on the spirochetal origin of multiple sclerosis may, in doubtful cases, justify the treatment of this disease both with mercury and neoarsphenamine, both of which have been tried by various observers with more or less beneficial results.

CHAPTER IV

Pathology of Multiple Sclerosis. The General Pathological Studies in the Pathogenesis of Multiple Sclerosis, the Locations of Lesions with Respect to Symptoms and an Investigation of the Axis Cylinder in Its Relation to Multiple Sclerosis

This chapter deals with the known pathology of the disease in general, its relation to the development of symptoms, and the present situation of the knowledge of the pathology of the axis cylinder.

The pathological studies in the pathogenesis of multiple sclerosis is presented by Dr. George B. Hassin of Chicago and Dr. William G. Spiller of Philadelphia.

The location of lesions with respect to symptoms is discussed by Dr. Edward W. Taylor, of Boston.

An investigation of the axis cylinder in its relation to multiple sclerosis is reported by Dr. Joshua H. Leiner of New York City.

Pathological Studies in the Pathogenesis of Multiple Sclerosis

George B. Hassin, M. D.

The present contribution represents a brief review of the histopathological changes in multiple sclerosis studied in material from 13 cases. Two cases came from the neurological service of Cook County Hospital, 2 were furnished by Dr. Peter Bassoe of Chicago, 1 by Dr. Theophil Klingmann of Ann Arbor, Michigan and 8 by Dr. Alfons Jacob of Hamburg, Germany. To these gentlemen I wish to express my gratitude for their kind cooperation.

In addition, 4 other cases were studied, 2 apparently normal cords, 1 cord from a case of capsular hemiplegia and 1 from Recklinghausen's disease, and the findings contrasted.

The best known and the most notable characteristic feature of multiple sclerosis is the so-called patch of sclerosis. Scattered throughout the central nervous system and varying in size and form they preferably affect the white substance, its long or short nerve fibers; they may be symmetrical or asymmetrical and may invade even the peripheral nerves (Strahüber, Schol). Wherever located, whatever the

FIG. 1. Eighth thoracic segment. Patches in the posterior columns, the right lateral column and in the right posterior horn. The transition zone in the posterior columns, between the patch and the normal-looking remnants of Burdach columns, is very marked. Weigert-Pal × 13. (*Arch. Neurol and Psychiat.*)

size or age (young or old), there can be discerned in a patch many nerve fibers in fairly good condition. A great many are merely deprived of myelin, appearing as naked axones (demyelinated nerve fibers); some are covered with myelin but partially, while others show a destruction of both the myelin and axone, exhibiting a state of Wallerian degeneration.

These three pathological features—apparently healthy fibers, fibers totally or partially demyelinated and fibers in a state of Wallerian or secondary degeneration—occur not only in the patches themselves, but *also in parts of the central*

nervous system which show no visible patches whatever. Even an ordinary stain, that of Weigert-Pal, for instance, brings out some of these features. Thus, Fig. 1 distinctly shows an old patch involving the posterior columns of the spinal cord where it appears as a pale island. Upon closer examination, with a hand lens or a microscope, one can discern in the colorless island a number of well-preserved fibers in the shape of black dots. These represent a transverse section of normal nerve fibers separated from each other by empty spaces.

Between the pale patch and the normal-looking lateral columns there is an area containing a much greater number of nerve fibers of normal appearance. Such an area, termed intermediate, transitional, adjacent or superimposed, is generally looked upon as a young, undeveloped patch, the further growth of which has been prevented by death. At any rate, an ordinary stain conveys the impression that an old patch grows by gradual spreading in width, not respecting the neighboring tissues—the glia, blood-vessels or the septa. It is also assumed that small plaques, gradually increasing in size, coalesce to form a larger focus which occasionally may cover the entire width of the spinal cord.

A much better idea as to the origin of a plaque, its growth and its relationship to the neighboring structures may be gathered from specimens stained with the methods of Marchi, Bielschowsky, Mallory-Jacob, Alzheimer-Mann, and especially with the combined staining methods of Marchi-Alzheimer-Mann or Bielschowsky-Alzheimer. The latter method brings out with remarkable clearness the various healthy and pathological structures.*

Fig. 2, a photomicrograph of a longitudinal section of an apparently *healthy* area stained with Bielschowsky and counterstained with the method of Alzheimer-Mann, shows very well the axones, the myelin and the glia. The axones show no particular changes, but the myelin sheath is tume-

* This combination stain has been described by me in a contribution on histogenesis of syringomyelia (*Arch. Neurol. and Psychiat.*, March, 1920, v. 130). In brief it is as follows: Bielschowsky's sections not impregnated with gold go into a solution of phospho-molybdic acid (about thirty to sixty minutes) then in Mann's mixture (1 per cent solution of methyl blue eosin), differentiated in 95 per cent and absolute alcohol.

fied, forming a broad swollen band around the well-preserved axones. In many places the myelin appears fragmented, broken up into globules and droplets. Under the oil immersion there can be observed in the myelin more or

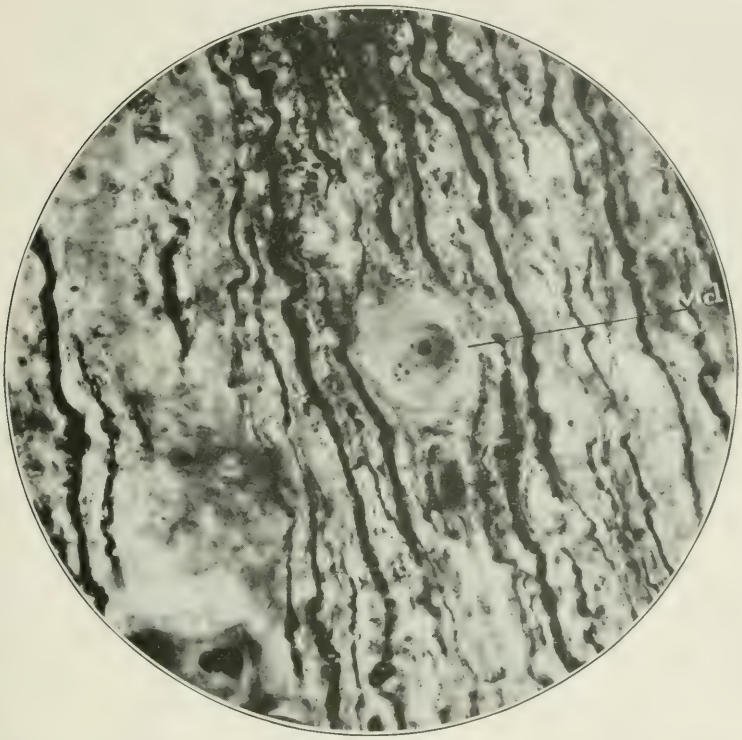

FIG. 2. Longitudinal section of normal looking remnants of Burdach columns. The black irregular lines are axones; the surrounding myelin (M.M) is either swollen, or shows minute globules (Elzholz bodies). Many of the black globules are parts of the axones which had been irregularly cut. In the center a *myeloclast* is seen within a large vacuole (Mcl). Use a hand lens. Bielschowsky-Alzheimer-Mann stain × 560. (*Arch. Neurol. and Psychiat.*)

less wide meshes giving the myelin a reticulated or fenestrated appearance, as if it consists of numerous holes through which the axone can be distinctly seen. The distended meshwork of the myelin sheath frequently breaks down resulting in the formation of cavities, so-called "Lücken" (Fig. 3).

The Marchi stained specimens, especially when counterstained with Alzheimer-Mann's or Mallory-Jacob's methods, exhibit, in addition to the marked swelling and fenestration of the myelin, numerous small black structureless droplets (Elzholz's bodies) scattered along the axone and

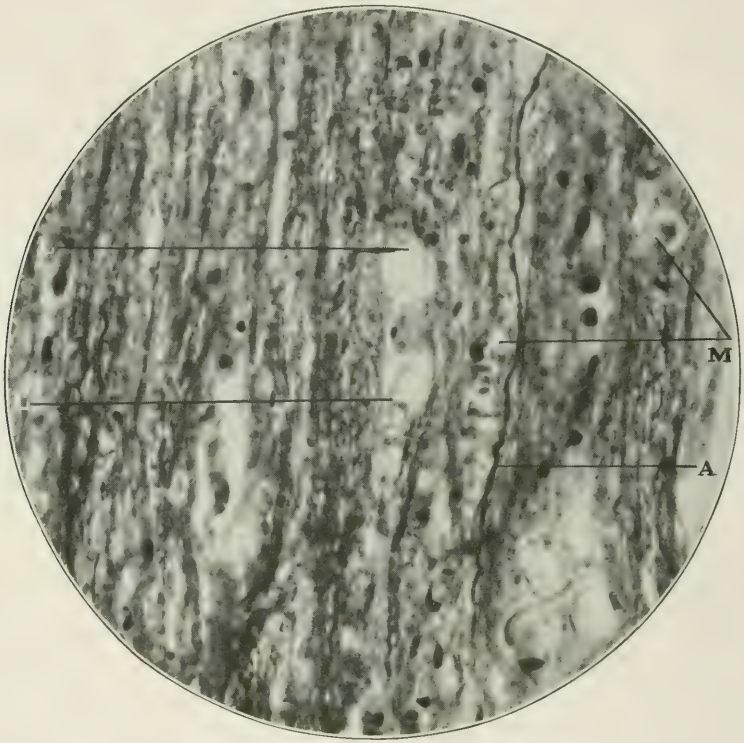

Fig. 3. Longitudinal section of a "normal" area. A, Axone; M, Myelin, broken up into globules (Marchi globules); L. L., "Lücken"—crossed by an axone. The tissues between the axones are glia fibers and glia nuclei (dark round bodies). Bielschowsky-Alzheimer-Mann stain × 450. (*Arch. Neurol. and Psychiat.*)

intermingled with fragments of broken up myelin. The myelin fragments may be of smaller or larger size, are made up of concentric layers, stain dark brown or black with osmic acid and are known as Marchi's globules (Fig. 3, *M*).

The outlined changes—swollen fenestrated myelin, its fragmentation with abundant formation of Elzholz's bodies and Marchi's globules in the presence of a well-preserved axone,

were found in all the 13 cases studied, outside the patch proper, in areas which with ordinary stains appeared perfectly normal. The changes are exactly similar to those described as periaxial neuritis by Gombault, Stransky and especially well by Doinikow in experimental *degeneration of peripheral nerves.* It would therefore be logical to assume that the earliest changes of multiple sclerosis obtain in the myelin and are *in the nature of a periaxial neuritis.*

The myelin changes, however mild, were always accompanied by marked proliferative phenomena in the glia tissue. The latter showed either as an increased number of glia fibers filling up the spaces between the parallel running, swollen nerve fibers, or as large glia nuclei, rich in chromatin, invested by a visible, well developed membrane and abundantly supplied with cytoplasm. The glia cells often appeared as large astrocytes (Deiters' cells) with numerous branching processes, breaking up into thin fibrils. Other glia cells, again, appeared greatly changed. They were lying within vacuoles, and presented large, somewhat broken-up granular cell bodies with an eccentric pycnotic nucleus and contained within their cytoplasm, minute droplets of lipoids. These gliogenous formations are myeloclasts (Fig. 2, *mcl*) described by Jacob in the earliest stages of secondary degeneration of central nerve fibers.

Equally marked were mesodermogenic changes—in the blood-vessels, pia and its septal prolongations. They all exhibited a pronounced hyperplasia and thickening, dilatation of the perivascular adventitial spaces which were packed with gitter cells and distention of the pial meshes.

Changes in the Intermediary Zone. Much more in evidence were the ectodermogenic (neurones and glia) changes in the intermediate area, or, where this was not well formed, in the regions adjacent to the plaque proper. The Marchi globules which began forming in the "healthy" areas were here more numerous. The axones were usually well preserved; sometimes they were slightly tumefied, finely granular, twisted and occasionally broken up into minute fragments. Both the myelin (or Marchi) globules and the fragments of the axones were enveloped by glia rings or were enclosed within gliogenous cell bodies containing

larger or smaller vacuoles and an eccentric chromatin-rich nucleus. These are Jacob's myelophages (Fig. 4) which, according to this investigator, pick up the broken-up nerve tissue and here transform it within their cell bodies into fat-like (lipoid) substances.

These lipoids are found in larger masses within a third type of gliogenous formation, generally known as gitter

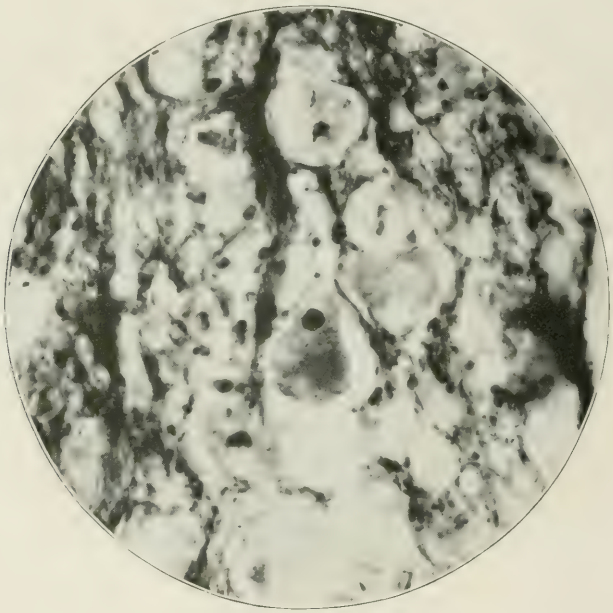

FIG. 4. A group of myelophages. The one, in the center of a large vacuole, contains within one of its own vacuoles an amyloid body (use a hand lens). Mallory-Jacob stain × 560. (*Arch. Neurol. and Psychiat.*)

cells or fat granule bodies (Fig. 5). The latter, as well as the myelophages, denote a further, more advanced, stage of secondary nerve degeneration than the stage of Marchi's globules and myeloclasts.

The gitter cells generally appear as fine reticular honeycombed bodies harboring within their delicate vacuoles the lipoids resulting from the digestive activities of the myeloclasts and myelophages. In human pathological material, it is possible to follow the transitions from a myelophage to a gitter cell which thus most probably

represents a further evolutional stage of a myelophage. Jacob holds that the latter, like the myeloclast, undergoes regressive changes, after the process of transformation of the broken-up myelin and axone is accomplished. Many

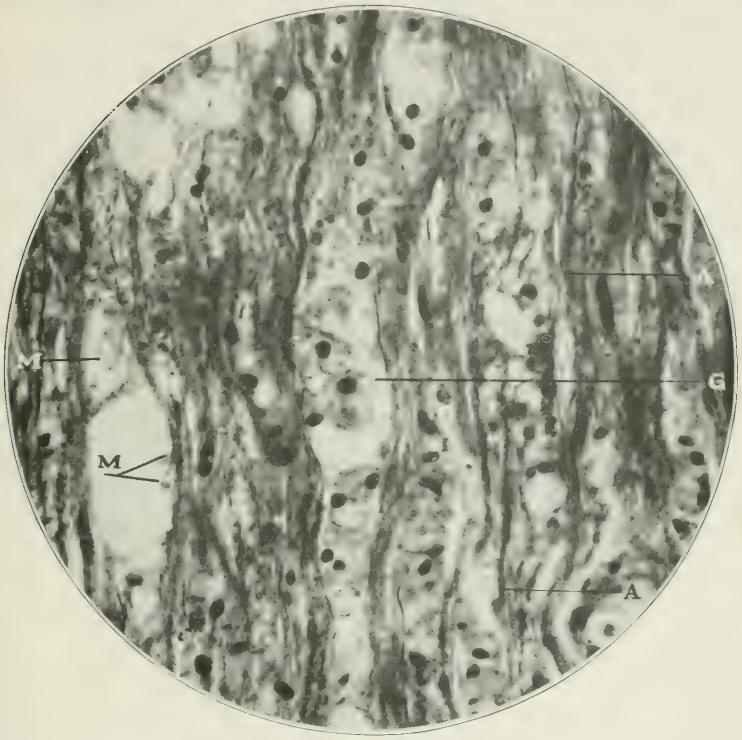

FIG. 5. Transition Zone, longitudinal section. The axones (A.A.) are fewer though well preserved. Many "Lüken" show fragments of myelin (M.M.); G-space occupied by gitter-cells (α and γ varieties); the black bodies are nuclei of gitter and other glia cells. Stain same as N3- × 300. (*Arch. Neurol. and Psychiat.*)

gitter cells still show a large vacuole with remnants of nerve tissue within (gitter-cells-α), some show large vacuoles packed with larger globules of lipoids (gitter-cells-β) and some show only minute vacuoles filled with very small droplets of fat. The cells of the last variety are round and appear freely scattered over the field of vision as well as in large masses around the vessels or between the glia fibers and even in the pia (gitter-cells-γ).

The presence of vast numbers of various fat-laden gitter cells gives the field a characteristic appearance (especially when stained with osmic acid, scarlet red (Fig. 6) and similar stains) described by some authors (Dawson, Klingman) as the stage of "fat granule myelitis." In general, such an area

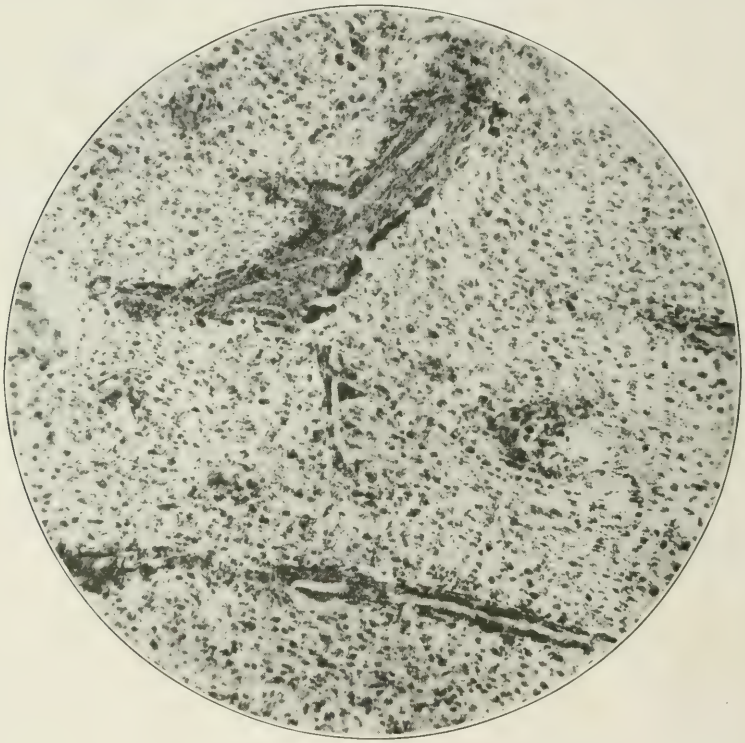

Fig. 6. Vessels infiltrated with gitter cells. The entire field is covered with fat laden gitter cells appearing as so-called "fat granule myelitis." Herxheimer scarlet red stain × 60. (*Arch. Neurol. and Psychiat.*)

in no way differs from that resulting from secondary degeneration, for instance, of the lateral spinal cord columns following internal capsular destruction.

The vessels in the intermediate area are more numerous, but show the same features as outlined above—the walls are thickened but usually dilated (Fig. 7) the dilated spaces containing an enormous number of gitter cells (γ-variety). In toluidin blue, thionin, hematoxylin-eosin, Van Gieson

and similar stains such infiltrated blood-vessels suggest at first glance an inflammatory condition, as if the infiltration consists of lymphocytes, plasma cells and similar hematogenous elements. Such an error can easily be corrected by having the specimens stained with osmic acid or scarlet red which will show that the infiltration cells are fat granule

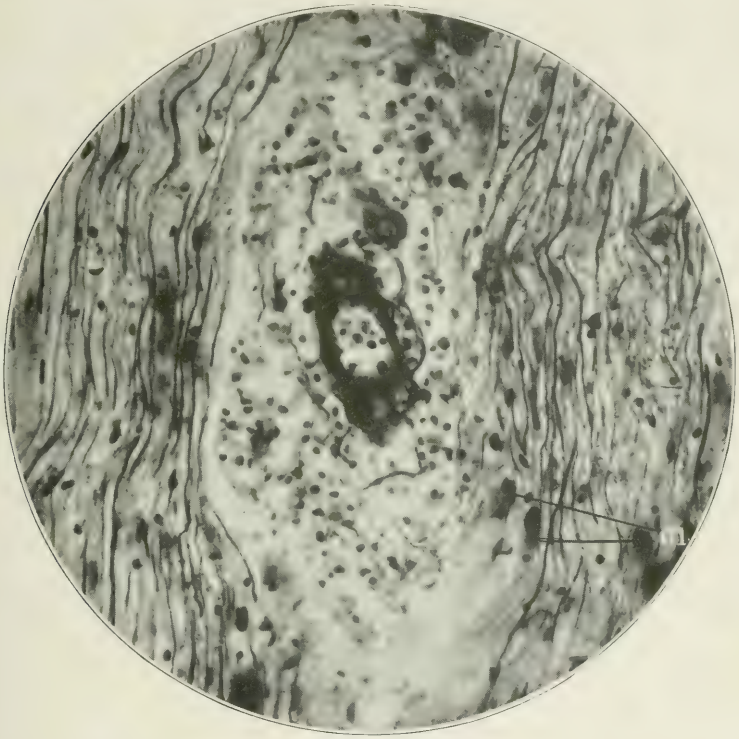

FIG. 7. Blood vessel with a dilated adventitial space (Virchow-Robin) packed with gitter cells. The surrounding axones are well formed; gl, protoplasmic glia cells which are here very numerous. Bielschowsky stain × 260. (*Arch. Neurol and Psychiat.*)

bodies (gitter cells). The latter are the principal constituents of the infiltrated adventitial spaces; lymphocytes, polyblasts, plasma cells were exceptionally rare, and even when present were greatly changed and degenerated. Polymorphonuclear elements did not appear at all.

Some blood-vessels or capillaries were devoid of infiltration; the adventitial spaces were not dilated but on the

contrary collapsed, thickened, often exhibiting numerous nuclei; the lumen, as a rule, was unobstructed, the endothelium very prominent.

The great number of *blood-vessels infiltrated with gitter cells* or possessing thickened walls is another characteristic feature of the transition zone. Yet even here one may find numerous

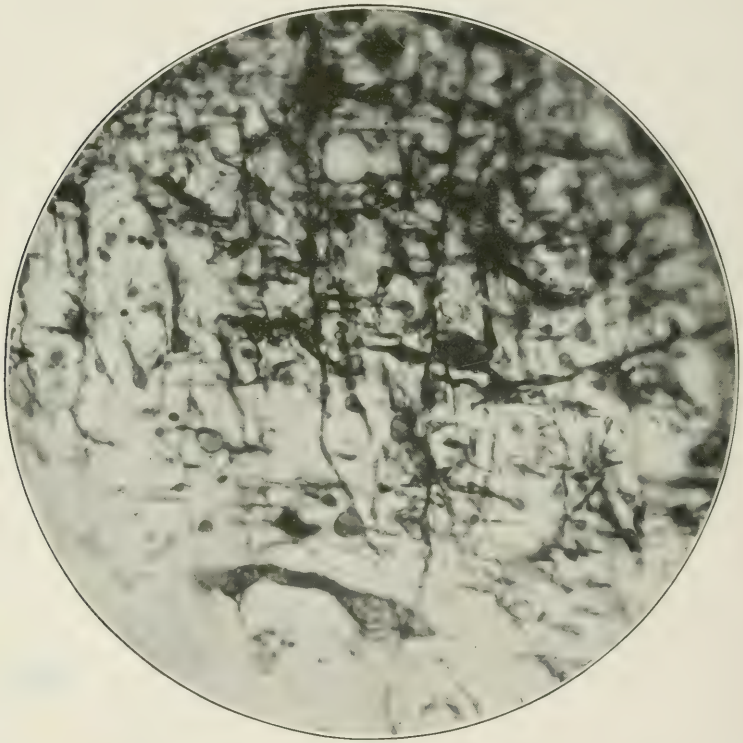

Fig. 8. Cortex: swollen myelin fibers; the lower nerve fiber shows fenestration and swelling; others are bulb shaped, spindle shaped or varicose. Frozen section stained with Weigert-Pal × 300. (*Arch. Neurol. and Psychiat.*)

Marchi globules, many nerve fibers, swollen and reticulated (Fig. 8) and even nerve fibers in fairly good condition. In short, the transition zone is made up of nerve fibers in various stages of degeneration, in no way differing from changes described by Jacob in secondary degeneration.

It is but proper to point out that a transition zone is often lacking, that is to say a patch frequently ends abruptly

without shading off into an apparently normal area. Yet, even in such instances there can be found, in the vicinity of the patch, nerve fibers in a state of advanced degeneration as outlined above (Fig. 8).

Patch of Sclerosis. After the broken-up fragments of myelin and axones have been transformed by the action

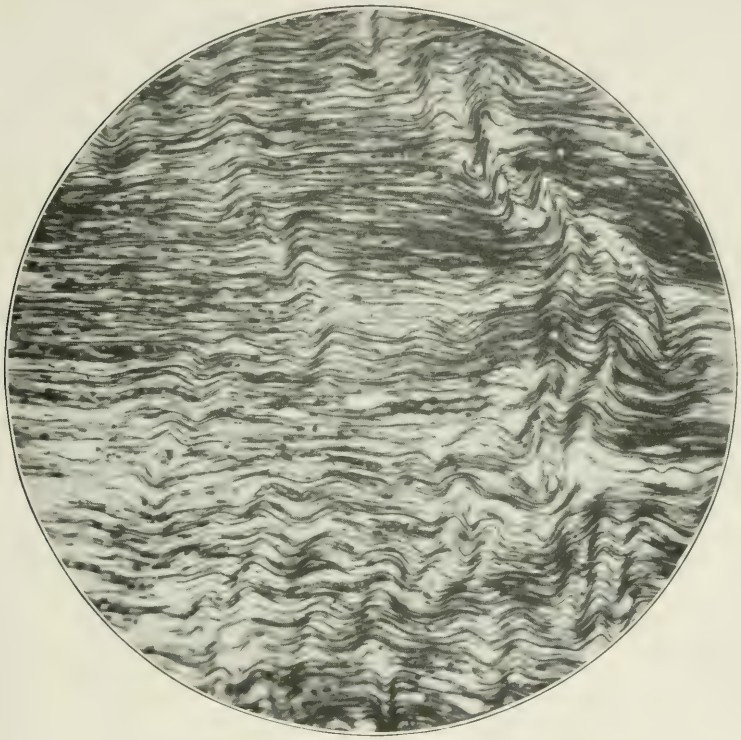

FIG. 9. Patch of sclerosis represented by a glia tissue scar. The undulating lines are glia fibers covered with numerous glia nuclei. Vessels are few; axones present but in very few numbers. Stain as N3 × 140. (*Arch. Neurol. and Psychiat.*)

of the myeloclasts, myelophages and gitter cells into lipoids and removed by the mesodermogenic tissues—blood-vessels and pia-arachnoid; in other words, after the damaged tissues have been cleaned up and freed of the scattered débris, the destroyed nerve tissue is replaced by a so-called tissue scar, a patch of sclerosis (Fig. 9). In its typical form, it consists of very thin neuroglia fibrils emanating from richly stained

oval or rod-like nuclei, and so thickly packed that hardly any interspaces can be discerned. In other instances, there is an abundance of cytoplasmic glia cells, homogeneous in appearance, possessing an eccentric chromatin-rich nucleus and a great mass of thin processes. Again, there are instances in which the glia scar *does* show interspaces. The size of an interspace is very small, one gitter cell being sufficient to fill it up. Scarlet red stain shows, in a glia scar, an abundance of minute, dust-like droplets of lipoids enclosed either within the glia nuclei and gitter cells or scattered over the surface of these cells.

Notwithstanding such severe destruction a stray nerve fiber covered with myelin may be encountered even in such deserted areas. More commonly, however, the scar tissue exhibits nerve fibers deprived of myelin, that is to say, nerve fibers represented by naked axones, running wave-like and parallel to the glial fibrils. They usually appear thinned, granular, distinctly fibrillar and often are difficult to differentiate from the glia. New formed or regenerated axones as described by Popoff, Strahüber, Doinikow and others could nowhere be found. Blood-vessels are, in the scar tissue, less conspicuous than in the intermediary area. They often show masses of lipoids within the adventitia which is usually thickened. Inflammatory phenomena, as in the previous stages, were absent.

The scar patch is thus to be considered the final stage of nerve degeneration which began as swelling and fragmentation of the myelin (Marchi-globule stage), continued as a stage of myelophage and gitter cell activity and ultimately resulted in the formation of a glia scar. The three consecutive stages of a patch evolution* in multiple sclerosis are thus entirely analogous to those observed in experimental secondary degeneration so well described by Jacob.

Pronounced and widespread as the nerve destruction is, the gray matter proper (of the spinal cord, the basal ganglia, and the cortex) is hardly involved. As a rule the cell bodies are normal but they may show phenomena of axonal reaction,

* Dawson speaks of six and Klingman of five stages which Klingman does not consider consecutive, while Dawson says the process does not always follow the same uniform course of development.

neurophagia, chromatolysis, pigment and fat accumulation, etc. Whatever changes the ganglion cells may exhibit, they are insignificant compared with those of the white substance and may justly be considered as secondary or accidental.

As secondary phenomena should also be considered the

FIG. 10. An enormously hyperplastic pia arachnoid; the vessels, mostly veins, are also hyperplastic; the brain tissue (the lower half of the picture) shows distinct small vessels with thickened not infiltrated walls. With the help of a hand lens, many infiltration cells can be seen in the meshes of the pia arachnoid as well as other changes. Alzheimer-Mann × 60. (*Arch. Neurol. and Psychiat.*)

changes displayed by the mesodermogenic elements—the pia-arachnoid, its septal prolongations, the blood-vessels and the chorioid plexus.

The pia-arachnoid was always found changed—thickened and infiltrated (Fig. 10). The thickening was closely associated with hyperplasia of its constituent elements

(mesothelial and connective-tissue cells), while the infiltration consisted of lymphocytes, plasma cells, polyblasts, gitter cells, many fibroblasts and also mesothelial cells. The majority of the infiltrative elements were greatly changed, the lymphocytes, for instance, showing as dark, pycnotic nuclei, without any vestige of cytoplasm, while

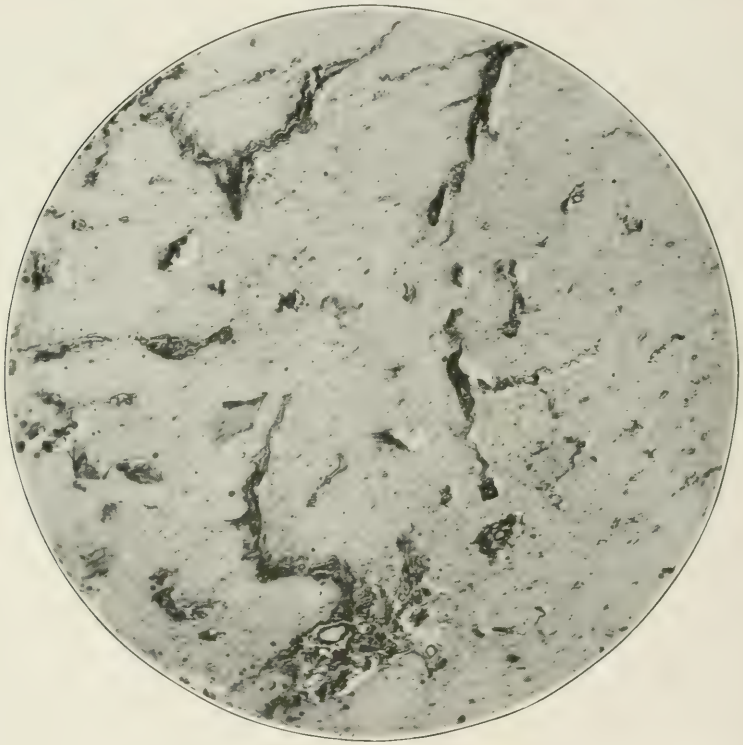

FIG. 11. Optic chiasm, covered with thickened, hyperplastic vessels and pial septa. Mallory-Jacob × 10. (*Arch. Neurol. and Psychiat.*

the plasma—as well as the gitter cells were broken up and disintegrated. In addition there were many red cells and macrophages packed with blood pigment.

The cellular elements and their fragments were freely scattered in the meshes of the pia-arachnoid, and in some instances, were so densely gathered that the affected region resembled that of a meningitis.

The same hyperplasia and thickening, but without marked infiltration, were present in the septal and cerebral prolongations of the pia, in the optic chiasm (Fig. 11) and in the blood-vessels. Scarlet red and similar staining methods revealed, in both the pia and its vessels, masses of fat drop-

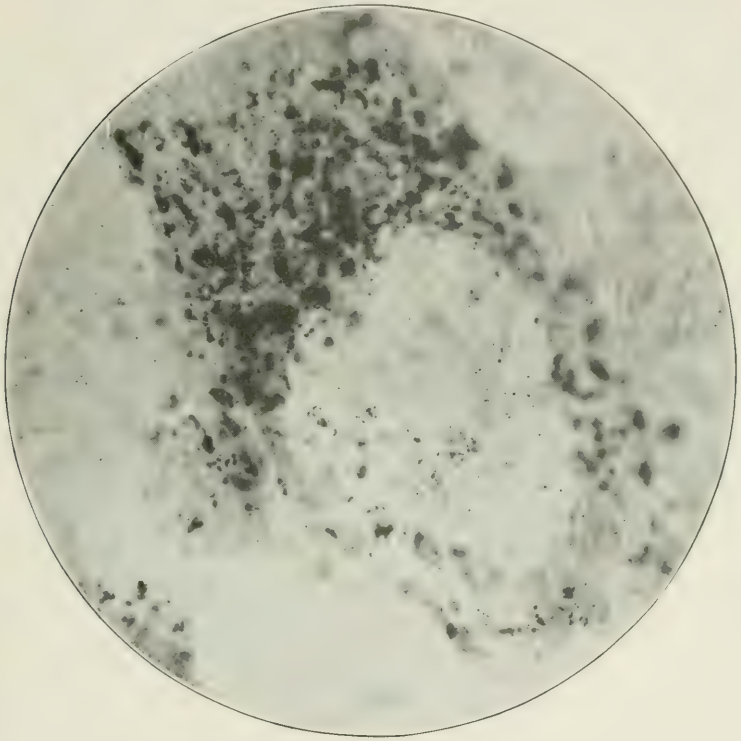

FIG. 12. Fat accumulation in the pia (surface frozen section stained with scarlet-red-hematoxylin of Herxheimer), × 275. (*Arch Neurol. and Psychiat.*)

lets enclosed within gitter and mesothelial cells. In some regions the pia was so densely packed with lipoid masses that these completely overshadowed other structures (Fig. 12).

As noted previously, vascular changes were present in apparently healthy regions, in the intermediate zone and in the patches themselves. In other words, regardless of the condition of the ectodermal tissues, the degree and extent of the lesion, the vascular changes were alike—distended

adventitial spaces packed with gitter cells, hyperplasia and thickening of the vessel walls. Some areas, especially in the cortex showed a greater wealth of capillaries, but no signs of budding, no regressive changes (such as hyaline degeneration, for instance), no marked thrombi formation, and but exceptionally, inflammatory cells (lymphocytes, plasma

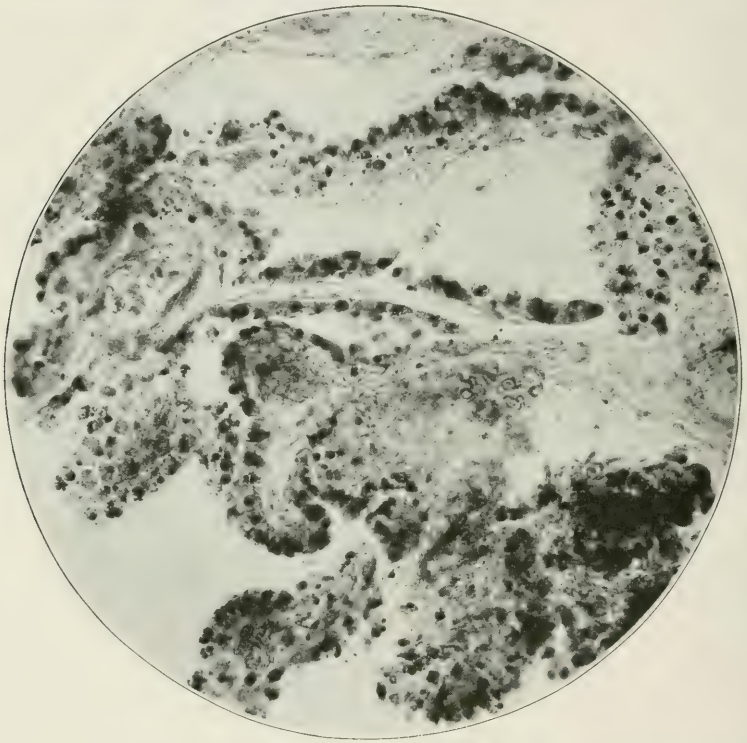

Fig. 13. Chorioid plexus. Fat globules in the tuft cells (black dots). Stain same as N12 × 230. (*Arch. Neurol. and Psychiat.*)

cells, polyblasts, etc.). Nor were hemorrhages with reactive phenomena found though occasionally pigment was present within macrophages found around smaller capillaries. (It was not possible to determine whether the pigment was fat or came from the blood.)

The chorioid plexus (Fig. 13) invariably showed thickened vessel walls, absence of inflammatory phenomena and many fat globules within the tuft cells.

General Summary. 1. Regressive and progressive ectodermogenic (neuronal degeneration and glia proliferation) associated with pronounced proliferative mesodermogenic changes (hyperplasia and thickening of the vessel walls, of the pia and the septa; dilatation of the adventitial spaces and their infiltration with gitter cells). 2. Absence of significant ganglion cell changes, of inflammatory phenomena and of any relationship of the ectodermogenic changes to the territorial blood supply. 3. Abundance of lipoids in the pia-arachnoid and the chorioid plexus.

Discussion. Of the foregoing phenomena the most striking are the ectodermogenic changes. They primarily show as a neuronal degeneration which goes through the same successive stages and obeys the same laws so well brought out by A. Jacob in experimental secondary nerve degeneration. He showed conclusively that the various morphologic glia changes—the formation of cytoplasmic glia, myeloclasts, myelophages, gitter cells, glia scars—are all secondary phenomena, following a primary medullary destruction. The morphology of the glia, the type of its constituent elements (cell bodies and fibers) thus depend upon the extent and severity of the parenchymatous lesions. In other words, the condition of the glia tissue denotes how far the nerve destruction has advanced.

The rôle of the glia, however, is not only to replace a destroyed parenchyma, but actively to remove it from the organism through the process of digesting the broken up myelin fragments and transforming them into harmless lipoid substances. When this is accomplished, the lipoids enclosed within gitter cells are carried to the adventitial spaces of the blood-vessels and thence to the subarachnoid space.

In both the subarachnoid and the adventitial spaces, the fat-laden gitter cells, as foreign bodies, cause an active proliferation of the constituent mesodermogenic or adventitial elements resulting in distension of the connective-tissue meshes. With the removal of the invaders of the blood-stream, the hyperplastic connective tissue of the blood-vessel walls and the pia collapse and shrink thus causing their thickening. The shrinking of the vessel walls may be so

extreme as to cause a complete or partial separation of the vessels from the surrounding glia tissue and lead to formation of so-called His spaces, designated by Nissl and his school as *Schrumpfräume* (contraction spaces); or the shrinking may be gradual and lead merely to the rarefaction of the adjacent glia with distention of its meshes, in short to sieve-like or "areolated areas." Such conditions (His spaces and areolated areas) have been considered by Borst the primary, essential cause of a patch formation. Without going into lengthy discussions of such a view I wish to point out that similar conditions also occur in any brain, whether normal or pathological, and that in multiple sclerosis the spinal cord, so rich in patches, does not show them at all. The phenomena outlined as observed in the adventitial lymph spaces, in the pia, in the perivascular areas, are purely secondary or accidental. They are found in areas devoid of patches and may be absent in regions profoundly changed, for they are due to the harboring of the destroyed parenchyma while on its way from the focus of destruction to the subarachnoid space. Distended adventitial spaces packed with gitter cells occur in any pathological condition in which secondary degeneration is the principal feature, as, for instance, in amyotrophic lateral sclerosis, subacute combined cord degeneration, secondary cord degenerations, etc. In short, the vascular, the pial and perivascular changes are not specific for multiple sclerosis and therefore cannot be considered the cause of the patch formation, its growth or dissemination. Nor does the patch follow the course of a blood-vessel as Dawson and others have shown. Dawson, for instance, studied small foci of sclerosis serially throughout their whole extent and came to the conclusion that they do not coincide with the vascular areas.

As the principal or primary changes are parenchymatous and are confined to the nerve fibers, while those in the glia and mesodermogenic elements (vessels, pia, its septal prolongations) are secondary, it follows that were it possible experimentally to produce multiple sclerosis, connective-tissue changes would be found, but as purely accidental, non-essential phenomena. So far experimental multiple sclerosis has not been produced, nor is it possible to produce this

disease either by interference with the blood supply or by irritation of the spinal cord.

Attempts to produce multiple sclerosis by injecting (intravenously, subcutaneously, intraperitoneally) spinal fluid from corresponding patients are theoretically fully justified. For such a cerebrospinal fluid discharged into the subarachnoid space is saturated with the products of catabolism or toxines which are the most probable cause of this morbid condition. The histopathological findings are certainly quite typical of a toxic, not a microbic lesion, and do not resemble the lesions resulting from disturbed blood circulation.

Vascular disturbances, in the nature of embolism and thrombosis, may produce foci of necrosis with subsequent formation of foci of sclerosis. But such secondary sclerotic foci have very little in common with those seen in multiple sclerosis. The same is true of the patches resulting from local irritation of the spinal cord substance. Thus, Leyden, by injecting Fowler's solution into the spinal cord of dogs, produced what he thought to be patches analogous to those seen in man and he concluded that multiple sclerosis is the result of a myelitis. Westphal discussing Leyden's experiments justly remarked that not every patch is to be considered the result of a previous inflammation.

In other words, patches occurring in the central nervous system may be of various origins. The Weigert-Pal stain, for instance, may show patches in cerebrospinal syphilis, disseminated encephalomyelitis, general paralysis of the insane, arteriosclerosis of the brain, traumatic cord and brain lesions, in short, whenever and wherever the parenchyma is directly involved. The above morbid conditions may, clinically and pathologically, so much resemble multiple sclerosis, that they have many times been mistaken for it both by clinicians and pathologists. The patches in the foregoing diseases, however, greatly differ from those seen in multiple sclerosis. Some will show inflammatory phenomena, as in encephalomyelitis; some will exhibit areas of softening, or, in addition to glia changes, is marked connective-tissue proliferation (in syphilitic lesions), etc. In short, they will exhibit phenomena entirely foreign to the conditions seen in multiple

sclerosis, and, on the other hand, there will be lacking the characteristic features.

For multiple sclerosis has *a pathological constant in its pathogenesis*, the changes starting as tumefaction of the myelin which, followed by the destruction of the axone, ultimately results in secondary degeneration. In short, they begin as a periaxial neuritis and end as Wallerian degeneration. The disease constantly affects new fibers which ultimately become replaced by a glia tissue scar. It resembles only subacute combined cord degeneration and peripheral nerve lesions caused by lead, alcohol or other poisons, described by Gombault, Stransky and especially well by Doinikow.

Multiple sclerosis also resembles a peculiar morbid condition which I am now studying, in which the dominant feature is also a degenerative process but in which the changes are limited to the second stage.

Conclusions. 1. In multiple sclerosis there are definite early changes in the form of widespread swelling of the myelin substance.

2. The myelin alteration is an acute and early manifestation with the formation of a waxy patch.

3. The glia undergoes changes later.

4. The pathological changes are primarily ectodermogenic, the mesodermogenic tissue participating in the alterations of the disease secondarily.

5. Vascular and septal changes are present, but are accidental phenomena.

6. Theoretically it is possible to produce the changes of multiple sclerosis without concomitant changes in the connective-tissue elements.

7. The patches of sclerosis are not representative of territorial areas in relation to

(*a*) the arterioles
(*b*) the venules
(*c*) the perivascular lymph drainage.

8. The lesions of multiple sclerosis cannot be produced experimentally either by interference with, or irritation of (*a*) the vascular supply, or (*b*) the spinal cord.

The following questions submitted to Dr. Hassin before the Commission, together with the answers to them, are here reported verbatim.

Dr. Hassin: The best known pathological feature of multiple sclerosis is the patch occurring throughout the central nervous system. Patches may also occur in various other diseases, such as cerebrospinal syphilis, general paralysis of the insane, encephalitis, traumatic cord lesions, etc., but these patches resemble the patches of multiple sclerosis only grossly; in other words, the similarity is superficial. The histological features are quire different. The patches in each disease have their own individuality. In multiple sclerosis the specific feature is formation of glia tissue, and that is so specific that early investigators, like Charcot, consider the glia feature as first, everything else being secondary.

Strümpell went further and claimed that there is a developmental anomaly of the glia tissue. Rindfleisch and a great many other investigators claimed that the principal feature of multiple sclerosis is not so much the change in the glia as the vascular disturbance, though they did not deny that the glia may participate in the process.

Leighton made it still simpler and declared that there is no such thing as multiple sclerosis; that every case of multiple sclerosis is a myelitis. Borst was not satisfied with the vascular theory and added changes in the lymphatics.

There are a great many other theories, but I will mention only one that was promulgated by Adamkiewicz and was somewhat timidly supported by Reddick, Hoover and Saunders. This minority claimed that the main features of multiple sclerosis are parenchymatous lesions, that they are the primary lesions and everything else is secondary.

I studied about 14 cases of multiple sclerosis and came to certain conclusions. Some of my findings I will demonstrate with lantern slides and I think you will be able to draw your own conclusions as to the real pathology of this disease. (The lantern slides were shown.)

The primary phenomenon is displayed in the myelin. If it were not for the myelin, there would not be any proliferation of adventitia or thickening of the myelin. One may find an occasional lymphocyte or plasma cell in the brain tissue in some cases, but they are all considered accidental phenomena.

The essential feature of multiple sclerosis is a degeneration of the myelin. What causes this degeneration, I do not know. It is cer-

tainly not an organism, because if the process were due to them, there would be degenerative phenomena, not in the nerve fibers but in the cell bodies. In addition, there would be inflammatory phenomena. Nothing of the kind occurs in multiple sclerosis. There would probably be the same thing as one sees in general paresis. Nothing of this kind occurs in multiple sclerosis, and those cases of multiple sclerosis that have been described by many very good pathologists as containing or showing inflammatory phenomena have not been cases of multiple sclerosis at all. That is what the pathology teaches us. The pathologist shows that in multiple sclerosis we have to deal with a degenerative process, and as regards all these toxic processes that are present it follows that the further studies of multiple sclerosis must be confined to those of the spinal fluid. Studies of the spinal fluid will bring out not only what multiple sclerosis is, but also how to diagnose it scientifically and how to treat it. I refer to biological and pathological and serological studies of the spinal fluid. They will aid us very materially in the diagnosis and treatment of this disease.

Dr. Meyer: How are we to understand that in the main we do not hear anything said about the secondary degenerations, in conditions which are described to us as complete scars, devoid even of axis-cylinders?

Dr. Hassin: The experimental studies of Jacob showed that when a nerve degenerated, the ultimate result is a glial scar. He proved that it occurs in from eighty to one hundred and eighty days, but not before eighty days. In his experiments on rabbits, monkeys and cats, he showed definitely that these scars are the ultimate result of nerve degeneration, as I demonstrated here. These also occur in subacute combined degeneration.

Whenever there is degeneration in multiple sclerosis, there is a scar-tissue formation, provided degeneration has had enough time to develop.

Dr. Meyer: I am not concerned so much with the degeneration *in loco* as with the degeneration which is bound, according to our experience, to occur beyond the focus, concerning which matter Dr. Hassin did not give us any information. We would expect secondary degenerations and not only degenerations *in loco*.

Dr. Hassin: All these degenerations are secondary, but they begin in the myelin.

Dr. Meyer: Dr. Barker suggests that I call it ascending and descending degeneration.

Dr. Hassin: In multiple sclerosis, the degenerations are confined to single degenerations and they begin in the myelin, just as in peripheral neuritis produced experimentally, as instanced in lead-

poisoning, it begins in the myelin and is followed by degeneration of the axone, and so forth. That is called secondary degeneration.

Dr. Meyer: It seems to me that there are foci in multiple sclerosis; there are those conditions which we speak of as plaques. As soon as we have a destruction of the nerve element, which includes not only the myelin sheath, but the axone, and thus a complete wiping out of the nerve fiber, we look for and expect degenerations of the whole system. I suppose to some extent those things do exist; but to such a restricted extent that it is extremely difficult to harmonize the description of complete scars, deaxonized, as it were, without an obligatory tract degeneration.

Dr. Hassin: In other words, if we have an extensive scar formation, we ought to have the same extensive scar formation below and above. In all cases this obtains. As a rule, a scar does not show all the fibers to be degenerated. There is a fundamental rule in multiple sclerosis, that degeneration is confined to single fibers, not to systems of fibers, and one will always find in scars which are not very old a great many fibers and axones preserved.

Dr. Tilney: Dr. Hassin has called attention to the fact that this process is essentially a degeneration in the axone. Now, if that is the case, what is the condition of the nerve cells with which these axones must be naturally connected?

We expect, of course, to find many of the tract cells involved in the cord, but it is almost unthinkable to believe that none of the cells in the gray matter would be without pathological change under such an extensive degenerative process in the axone.

Dr. Hassin: The cells in the cortex, and in the spinal cord, do show change; they have nuclei displaced, and so forth, but one has to search for them; it is necessary to look over hundreds and hundreds of specimens before the plaques where those cells are destroyed, are found.

Dr. Sachs: May I ask Dr. Hassin whether his experience covers some of the cases of multiple sclerosis that have accidentally died early in the course of the disease, and whether his experience warrants him in stating that he is certain that even in earlier stages of multiple sclerosis there is no inflammatory reaction of any sort?

Dr. Hassin: The youngest case I had was two years old; but every multiple sclerosis has freshly involved areas; every one of them.

Dr. Sachs: Even the very chronic cases?

Dr. Hassin: Even in the chronic cases early areas of disease are found; also fresh areas, and areas, where the process is older, and very old areas. One finds everything in multiple sclerosis. That is

the difference between multiple sclerosis and myelitis. In myelitis no new areas of disease are forming, but in multiple sclerosis the areas are forming all the time until the patient dies.

Dr. Hunt: I would like to ask Dr. Hassin if he has studied cases with the symptomatology of multiple sclerosis, but in which the lesion has been that of an acute disseminated inflammatory reaction?

Dr. Hassin: All my cases were sent to me. I had only 1 case of my own that I could follow up, clinically, in the Carnegie Hospital, and that patient was in a dying condition when he was sent to the hospital. I could not follow the acute cases at all, because there are no such cases.

Dr. Hunt: I mean cases that are called acute disseminated encephalitis or myelitis.

Dr. Hassin: I had no such cases.

Dr. Barker: Are there other conditions, outside of multiple sclerosis, in which myelin is attacked?

Dr. Hassin: Subacute cord degeneration so resembles multiple sclerosis, pathologically, that it is almost impossible to distinguish between the two.

Dr. Tilney: In order to make the record clear, will Dr. Hassin state for us the criteria of differentiation between the gitter cell and the plasma and wandering cells that sometimes occur in these perivascular spaces?

Dr. Hassin: Of course the gitter cells or the plasma cells are very small; it is impossible to differentiate them, unless the proper stain is used. Gitter cells will be black or red depending upon the stain if the plasma cells are fully developed, they have such a typical cytoplasm that it is impossible to confuse them with gitter cells. Gitter cells are vacuolated and they are larger as a rule. In doubtful cases I use different stains. That is the only thing that helps me out, if I want to be sure, but sometimes it is easy and sometimes it is very hard.

Dr. Barker: Can you explain why in the subacute combined degeneration the axones go in systems, whereas in multiple sclerosis they go as single fibers?

Dr. Hassin: It may be the nature of the fiber, about which we know nothing.

Dr. Hunt: Did you find any correlation of the plaques with vascular areas, or with the cerebrospinal fluid, in relation to the ventricles or the subarachnoid spaces?

Dr. Hassin: The plaques have not been in relation to the vascular changes. For instance, the case I demonstrated shows vascular changes. The axones are normal. The spinal fluid does

not have anything to do with the plaques either, because we may find marked meningeal thickening and yet the areas surrounding are all normal.

Dr. Taylor: Is it not true that in the combined degeneration, so-called, that also is never truly systemic? I mean it is always diffuse, outside the lesion, practically outside the actual system tract; is it not?

Dr. Hassin: That is true. The degeneration affects more fibers than in multiple sclerosis. In other words, subacute combined degeneration is more powerful than multiple sclerosis, more striking than in multiple sclerosis, but it is the same thing, pathologically.

Dr. Hunt: Did your studies include also cranial or peripheral nerves, to see if a reaction existed there similar to that found in the central nervous system?

Dr. Hassin: I found a few roots, and those roots showed very similar changes. The work of Stryhoefer showed that in the roots and in the peripheral nerves the changes are the same.

Dr. Timme: Would not the vessels in other parts of the body, in tissues other than the nervous system, show evidence of a toxin?

Dr. Hassin: There is no reason for them to show that, because the vessels that show them in the brain, have to remove the lipoids; those in the liver do not have to remove them. The brain vessels show the spinal changes because they are loaded with these destroyed tissues. They are dangerous and they remove them. The vessels of the kidneys or lungs do not have to remove lipoids.

Dr. Timme: How about the vessels from the subarachnoid space?

Dr. Hassin: Those lipoids which form in the brain go to the subarachnoid space, from there they go to the blood, and are eliminated.

Dr. Spiller: Have you studied the normal tissue in order to determine the process that is going on with the feeling that you were getting at the foundation of the process? Is it not possible when one studies normal tissue in a case that has existed, as you said your youngest case has, for two years, that one is studying reactionary processes and that even if one does get areas that seem to be in an earlier stage than other areas, what reason has one for concluding that those earliest areas which have existed at least two years, or perhaps less than two years, represent the primary process of the disease?

Dr. Hassin: Because in my case I compared these findings with experimental studies of secondary degeneration. I was guided by the work of Jacob, who followed the changes in the nerves and glia day by day in animals, and I followed them out with cases

of multiple sclerosis and compared them with the work by Jacob. If those changes are considered secondary degenerative, pathologically, why should not I consider these secondary? They are thoroughly similar.

Dr. Spiller: When you speak of myelin cells and gitter cells, am I correct in understanding you to place the gitter cells in a later stage than the myelin cells, and in what way do they differ, if they differ at all, from the older cells described by the German writers?

Dr. Hassin: Granular cells are the same as gitter cells. They are called gitter cells on account of their structure and because not all of them contain lipoids only. They are practically the same thing.

Dr. Spiller: Is it not possible that multiple sclerosis in some cases may be inflammatory, while certain types, as I have described, on account of the comparatively long duration of the process, do not show evidences of inflammation; that if we could have seen those cases in the earlier stages, we would have found evidences of inflammation; and that when one studies adjoining areas, hunting for such evidences, and does not find them, that one is depending upon a reactionary process and not on the primary process of the disease?

Dr. Hassin: In multiple sclerosis, inflammatory processes in the spinal cord are never found, and even those who adhere to the inflammatory theory claim that they may be accidental, because many cases of multiple sclerosis die from accidental infections, etc.

I could never see any remnants of inflammation in the 14 cases, from which there were made thousands and thousands of specimens, stained with all kinds of stains. I hunted for them, looked for them, but I could not find them.

Dr. Spiller: You have said that the process was primarily a degeneration of the myelin. Why does this toxin not equally affect the axones of the cylinders, since you find the myelin greatly degenerated and the axones not equally degenerated? Have you any reasons to explain why the myelin is so greatly degenerated and the axone degenerated to a much less degree?

Dr. Hassin: They claim that the vulnerability of the myelin to destruction is greater than that of the axones. Until we know the precise toxin, I do not think we shall be able to answer this question.

Dr. Hunt: Is there any explanation for the group of cases, not large perhaps, but which are described in the literature, in which the lesion which is described exists in combination with acute disseminated inflammatory lesions; a type of multiple

sclerosis in which the patient dies in a relapse and which combines an old and a recent lesion?

Dr. Hassin: Yes, such cases have been described, but they proved to be encephalomyelitis. Hennebert recorded a case that Oppenheim described as multiple sclerosis, but Hennebert did not like the name of acute multiple sclerosis, so he introduced the name of malignant multiple sclerosis. Both authorities admit that those cases are not multiple sclerosis but disseminated myelitis, since they show degeneration of systems.

Dr. Hunt: But there is a type described, in which the typical plaque of multiple sclerosis exists in combination with an inflammatory involvement.

Dr. Hassin: Yes, they call it multiple sclerosis, but it does not mean that it is multiple sclerosis.

Dr. Meyer: Dr. Mussen, who has had an opportunity to examine concussion cases from the war, suggests that the pictures which Dr. Hassin has shown are identical with those that he has observed in those cases. I suppose in any such claim one might raise the issue, whether, after all, one would not find evidences of primary destruction and then a reaction to that primary destruction in keeping with the process. I do not consider that point of similarity as important as these general questions: To what extent have you, from your own experience and from the literature, paid any attention to the distribution of the patches; to what extent have you made an attempt to determine out of the nature of the patches, the question whether we can talk of any toxin? To what extent has it been possible to determine whether the lymph circulation might have something to do with the process?

In the only case of multiple sclerosis that I have had a chance to examine, out of a very large autopsy experience, I was very much struck by the distribution of the patches, especially in relation to the corpus callosum and to the ventricle. There was quite decidedly a preponderance of large patches right under the splenium. I know perfectly well that that does not hold for the spinal cord, because there the patches are very uneven. Nevertheless, it would seem to me that before we speak of any diffused toxin, we ought to try to make an effort to determine whether there is anything in the lymph circulation, if not in the vessels, that might give us a clew as to why there are circumscribed patches. The condition underneath the lateral ventricle, and especially the splenium of the corpus callosum and its radiation were altogether too striking to be overlooked, and to suggest the possibility of some fluid circulation outside the blood-vessels that ought to receive consideration.

Another point that I would like to take exception to is the explanation of the secondary meningitis in these cases, as if it were just the effect of the accumulation of fat materials that go there and undergo a reduction. I do not think that is so; I think that the meningeal thickening is absolutely independent of the amount of fat accumulation.

Dr. Hassin: The meningeal changes in multiple sclerosis are of the same type as in subacute combined cord degeneration. In every type in which you have an accumulation of fat substance in the meninges, you will have such an active phenomena. Of course, occasionally it is not a meningitis; I call it a reactive meningeal thickening.

As to the traumatic lesions, I am not surprised that they look like patches in multiple sclerosis, because in Jacob's work he found that to be true, but in traumatic lesions of the spinal cord and brain you will find hemorrhages which you do not find in multiple sclerosis. In multiple sclerosis you will find them only in exceptional cases.

As to the distribution of the patches, I think the statement, that patches are more numerous around the splenium, and so forth, is an exaggeration. I hunted for them and I could not find them. Why those patches should be there, I do not know. Why should certain fibers be picked out and become degenerated and the neighboring fibers should not? Why some fibers are more resistant than others, I do not know. I was fortunate to find something that would explain the pathology of multiple sclerosis, without going into such deep problems as to why a certain system of fibers should be destroyed in a certain area—in the corpus callosum more than the spinal cord. It is entirely impossible to explain this.

Dr. Meyer: I do not believe that Dr. Hassin, or anybody else, is able to prove that when he finds isolated patches of degeneration, that that is anything but secondary degeneration. The well-defined patches await explanation in some way and are not going to be explained by toxic conditions, but will have to be explained by other determinants in multiple sclerosis.

Dr. Barker: In certain diseases of the central nervous system, in which there are multiple disseminated lesions, sometimes there are focal degenerations in the organs of the body, in the viscera, for example. I would like to ask if the visceral degenerations have been studied in the focal lesions?

Dr. Hassin: Strümpell and Millard are the only ones who speak about that.

Dr. Strauss: Dr. Friedman asks: Have you seen in multiple sclerosis any evidence of neurolytic swelling described by Wohlwil in combined sclerosis?

Dr. Hassin: It happens in multiple sclerosis in some cases, that the axone is swollen. This is similar to what occurs in subacute cord degeneration.

Dr. Taylor: Dr. Ayer asks: Is there any suggestion that this type of degeneration simulates the degeneration caused by metallic poisons as studied by you?

Dr. Hassin: No, it does not. Metallic poisons and organic poisons produce different reactions in the nerve tissue.

Dr. Timme: This question has been handed in by Dr. Rosett: In an inflammatory process we may account for remission of the clinical symptoms by the subsidence of the inflammatory process, but how can the clinical phenomena of remissions be explained when the pathological process is one of progressive degeneration?

Dr. Hassin: This progressive degeneration does not involve the different systems; it involves only some of the fibers.

Dr. Timme: The question is asked as to how can you explain the remissions?

Dr. Hassin: I do not explain the remissions; they are explained by others. The statement is made that the remission is due to the fact that when a certain patch of fiber is destroyed, the remission starts, and then another patch is destroyed. The actual symptoms are due to the process of destruction of the fibers.

Dr. Timme: Then why should there be a disappearance of some of the symptoms and immediate remission?

Dr. Hassin: Because if the fibers are destroyed, the process stops, so far as this system is concerned.

Dr. Timme: Then all the symptoms would remain from that original patch.

Dr. Hassin: The symptoms depend upon the location of the patch. If the patch in the lateral column is finally formed, the patient will develop a certain set of symptoms, until another patch in the lateral column forms and destroys another column. If the myelin is swollen, if many fibers have a swollen myelin, that would not cause any symptoms; the symptoms are brought on after the myelin is destroyed. That takes time.

Dr. Sachs: You have taken a decided stand on the one fundamental question we are interested in, namely, whether this was a degenerative or an inflammatory process. I understand your own conviction is that it is a degenerative disease.

Dr. Hassin: That is what my studies show.

Dr. Sachs: In any of your specimens have you discovered anything that you, as a pathologist, would have taken to be indicative of syphilitic disease?

Dr. Hassin: Nothing.

Dr. Strauss: In the course of Dr. Hassin's presentation he made a statement regarding the gitter cell being always indicative of a degenerative process. I do not think Dr. Hassin meant quite that.

Dr. Hassin: Yes, I did.

Dr. Strauss: I do not think Dr. Hassin meant quite that, because we see gitter cells in inflammatory processes; we find them in subacute epidemic encephalitis and we look upon the gitter cell as being a scavenger cell for the removal of products which may result from inflammatory destruction. For instance, gitter cells are found after hemorrhage, and they occasionally contain pigment.

Dr. Hassin: Blood cells are found in hemorrhage, not gitter cells.

Dr. Strauss: But besides, we have found gitter cells demonstrated by the scarlet red stains in subacute epidemic encephalitis.

Dr. Hassin: In that case it means that there is a degenerative process combined with an inflammatory process.

Dr. Strauss: You cannot say that the gitter cell is only to be found in degenerative processes.

Dr. Hassin: You can say that, principally.

Dr. Strauss: You state that the adventitial proliferation is due to the presence of the gitter cells in the Virchow-Robin adventitial space. As I understand, the gitter cell is in that space merely, so to speak, in transit to the subarachnoid space. In subacute epidemic encephalitis, again, we can show proliferation of the adventitia similar to what you showed in some of your specimens; in some cases more marked than that, where the Virchow-Robin space does not show gitter cells. There may be other elements in the space. Do you not think that, just as Dr. Meyer pointed out in regard to the reaction of the meninges, the mere presence of the gitter cell ought not by its presence to cause a reactive change; that there must be another factor, possibly an action of a toxin or a toxic substance associated with that gitter cell, which would cause the proliferation, because, as I state, we see that proliferation in other diseases where there is an inflammatory and not a toxic process?

Dr. Hassin: A toxic process may play some rôle.

Dr. Strauss: Why should the presence of a cell of that type, which is, as you admit, purely a carrier of the last product of catabolism, be sufficient to cause a reaction in the cells of the adventitia?

Dr. Hassin: Because, in order to get into the adventitial space, the adventitial fibers have to proliferate in order to incorporate

those cells within. In the case of Bassoe's myelomeningitis, there is an enormous number of gitter cells in the spinal cord; we can prove by our sections that the adventitia envelops these tissues and transports them to the subarachnoid space.

Dr. Strauss: Your explanation of envelopment may be true, but it cannot be true in cases where we find the adventitia proliferated and no cells present.

Dr. Hassin: Perhaps there is some other process. The Virchow-Robin space sometimes is packed with lymphocytes and one cannot demonstrate this proliferation of these adventitial fibers.

Dr. Strauss: You know the lymphocytes can get out.

Dr. Hassin: I know how the gitter cells get in there and produce this proliferation.

Dr. Strauss: In the subacute combined sclerosis, which has been mentioned, is it not true that in that disease, when the very early stages are studied, the result is not the system disease primarily at all, but foci, very small plaques, similar to those which occur in multiple sclerosis; that the real system disease follows as a sequela of the focal pathological change?

Dr. Hassin: I studied 2 cases of subacute combined sclerosis.

Dr. Strauss: In speaking of remissions, and attempting to use that as an argument for an inflammatory origin of multiple sclerosis, is one not in as great a difficulty in explaining remissions of an inflammatory nature, where the pathological condition has caused destruction? For instance, in general paresis, there is an inflammatory process and destruction, and there are also remissions with alteration in the objective symptoms. Are you not in as great difficulty in explaining those remissions as you would be in explaining the remissions in degenerative processes?

Dr. Hassin: I was never interested in the question of remissions.

Dr. Strauss: I just wished to show Dr. Hassin that any deductions based upon the presence or absence of remissions could not throw any light as to whether the process is inflammatory or degenerative in nature.

Presentation by Means of Lantern Slides of the Lesions of Multiple Sclerosis

William G. Spiller, M. D.

Dr. Spiller demonstrated a number of slides presenting various lesions occurring in multiple sclerosis and showing the various parts of the brain affected. The implication of the tissue about the ventricles, the acute manifestations

of the disease as shown by the Marchi stain, the extraordinary symmetry of the lesions in some cases, the looseness of the neurogliar proliferation in certain cases, the implication of the nuclei of ocular nerves and of the fibers controlling the tendon reflexes, the atrophy of the temporal side of the optic nerve, etc., were all illustrated.

Dr. Spiller: I have pondered over this subject from various aspects for many years and I have been uncertain whether to attribute multiple sclerosis to a primary change of the "noble tissues" (using a French term), i.e., the nerve fibers, or whether to regard it as primarily a neurogliar proliferation. I have concluded that it is probably in most cases a primary change in the neuroglia.

The sclerotic patches are typical with the grosser stains in the case of epidemic encephalitis to which I have referred, I mean such as the Weigert medullary sheath stain. They have the sharp outline of typical multiple sclerosis. In the case of epidemic encephalitis to which I referred last year at the meeting of this society, there was only one patch, but one patch is enough to give certain indications of the process, and at last year's meeting I mentioned that having found one patch of sclerosis in epidemic encephalitis I believed other cases would be observed with numerous patches. Before the year was out such a case has been reported by me. In both these cases the patch definition was as sharp as in multiple sclerosis.

With a nuclear stain in the case of epidemic encephalitis with numerous patches, the cells are those recognized as characteristic of epidemic encephalitis, i.e., plasma and lymphocytic cells about the blood-vessels in great numbers and extending into the tissues. In these sclerotic patches there are masses of cells largely of a globular type, containing a single nucleus, such as are recognized as fatty granular cells.

I have asked the question whether the earlier findings in the sclerotic patches would not change so materially as to appear entirely different in the later stages. This has seemed possible to me. In the case of encephalitis with a single patch the cells are not nearly so numerous, and the patch has more the appearance of a patch in an old case of multiple sclerosis.

As regards the subacute case of multiple sclerosis, from which I have shown lantern slides, in areas of the cerebrum where the changes are still in an early stage, the patches are composed chiefly of glia cells and are different from the sclerotic patches in the spinal cord of the same case of longer date.

I believe there are cases of multiple sclerosis which are not entirely degenerative but show evidence of inflammation in perivascular lymphocytic infiltration, and this is in conformity with findings I made in Obersteiner's laboratory in 1893 or 1894 and which are referred to in one of the "Arbeiten" from his laboratory.

The following questions submitted to Dr. Spiller before the Commission, together with the answers to them, are here reported verbatim.

Dr. Strauss: In the case which you reported last year, was that patient observed before the attack of acute epidemic encephalitis sufficiently long for you to say that there was no antecedent multiple sclerosis?

Dr. Spiller: The brain in that case was sent to me from a distant city. Tumor had been suspected and operation had been performed. The history was sent to me and I had no hesitation in making the diagnosis of epidemic encephalitis from it before I had examined any sections. I have never seen a case, and I question whether anyone has, of multiple sclerosis with only one patch in the whole nervous system.

Dr. Strauss: In the case of encephalitis with numerous patches, was the antecedent history such that you could rule out the diagnosis of multiple sclerosis?

Dr. Spiller: I do not think there was anything in the symptomatology which would strongly suggest multiple sclerosis. The symptoms had begun only about three months before the patient's death. She was supposed to have been a healthy girl previously.

Dr. Strauss: In the case of subacute multiple sclerosis of two years' duration, is it possible that had this case occurred in an epidemic of encephalitis you might have regarded it as one of epidemic encephalitis from the beginning? Cases have occurred of epidemic encephalitis which strongly resembled clinically multiple sclerosis.

Dr. Spiller: That is true and such a case has been reported by Dr. Cadwalader.

Dr. Strauss: Could not one then regard your case of subacute multiple sclerosis as one of encephalitis because of the marked inflammatory reaction?

Dr. Spiller: That possibility should be considered. The case occurred before we had an epidemic of encephalitis in this country, but I should not consider it as one of encephalitis from the symptoms and pathological findings. The masses of cells in the cerebrum were composed of acutely proliferating glia cells.

Dr. Strauss: If you were to examine your specimens histologically without knowing anything of the clinical history, could you from your histological examination diagnose encephalitis?

Dr. Spiller: I should still form the diagnosis of acute or subacute multiple sclerosis. There is not the intense collar of lymphocytic and plasma cells about the blood-vessels which is so characteristic of epidemic encephalitis and the acute cellular proliferation within the tissue is of glia cells.

Dr. Hunt: I would like to ask Dr. Spiller whether, from his large experience with this disease, he would distinguish definitely from the pathological standpoint a degenerative type and an inflammatory type, or are the 2 types always present in combination but in varying degree?

Dr. Spiller: I have not felt that the inflammatory type in multiple sclerosis could be so sharply distinguished from the degenerative type as Dr. Hassin has done.

Dr. Mills: In connection with what to me was one of the most interesting parts of the presentation, that is, the vascular supply theory of the tendency to systematization, I would like to ask what might be termed a clinical question, one that has some relation to the preceding presentation, namely, whether this theory and this tendency to systematization may not be the explanation of all the varying clinical phases of multiple sclerosis, that of remissions, which was brought up here in connection with the last paper and which Dr. Hassin so very quickly dismissed. It seems to me that the pathological explanation of the clinical phenomena is that the differences, remission, relapse, advance in these cases are caused by the occurrence of circulatory or vascular toxic conditions which bring about what might be termed spurts in the symptomatology of the disease.

Dr. Spiller: Of course, the question of the relation of the disease to the blood-vessels is one that has been considered many years, and I do not think it is determined even at the present day; but I have been impressed particularly by the sections which I showed from a series taken from various levels of the same spinal cord, by the extraordinary symmetry in certain cases of multiple sclerosis, and, corresponding to the vascular distribution, as we believe it to be, of the spinal cord, the posterolateral supply as distinguished from the anterolateral supply. There are other cases, and I have sections from many such cases, which do not show this sharp correspondence between the vascular supply and the sclerotic patches. There is reason to think that the blood-vessels may play an essential part in the pathology of multiple sclerosis; and as Dr. Mills suggested, that fact would explain the symptomatology,

the remissions, recurrences, better than any other explanation that can be offered.

I have come to feel that multiple sclerosis is probably an acute disease and partly inflammatory, and is probably dependent in large part upon the vascular supply of the part affected. Possibly it is caused by some toxin circulating in the central nervous system.

Multiple Sclerosis: The Location of Lesions with Respect to Symptoms

Edward W. Taylor, M. D.

A correlation of signs and symptoms with lesions should be possible as in other disorders of recognized organic character. Certain difficulties present themselves; first, owing to the relatively nondestructive character of the pathological process no just parallel can be drawn between its apparent extent and the resultant signs and symptoms; in the second place, exact and painstaking correlations of lesions and symptoms have rarely been attempted in the now large number of clinically observed cases with subsequent autopsy. Writers in general have been content with general statements.

A disease process which manifests itself pathologically by perhaps a hundred or more lesions scattered indiscriminately throughout the central nervous system cannot adequately be described or pictured.

In many cases there appears to be practically no relation between the symptoms observed during life and the findings post mortem. As the autopsies have multiplied it has become increasingly apparent that a very large number of cases unsuspected during life have been demonstrated to be multiple sclerosis of typical pathological character. In view of our increasing knowledge, the assumption that perhaps next to tabes, multiple sclerosis is the most frequent organic disease of the nervous system, may not be an over-statement. The so-called *formes frustes* of Charcot are certainly far more frequent than the classical type of the disease. We still recognize a type form of the disease characterized by nystagmus, scanning speech, ataxic tremor of the intention

type to which may be added weakness with spasticity. This well-defined combination of signs occurs in no other condition in like degree.

The early loss of myelin and persistence of axones and cells must be held at least in part responsible for these characteristically irregular movements. Charcot definitely regarded this irregularity of movement as conditioned by an altered resistance to conduction in the sclerotic area. Erb, on the other hand, believed it due rather to the localization of the sclerotic patches than to any peculiarity of the pathological process itself, a theory which has gained in acceptance as the general knowledge of localization has increased. Dawson, for example, considers the hypothesis established that the incoordination results from interruption of or disturbance in the cerebello-rubro-thalamo-cortical pathway. The eye muscle involvement leading to nystagmus is likewise regarded as due to lesions about the ventricle, aqueduct, third nerve nucleus, Deiters' nucleus and doubtless higher levels as well. The tendency to spasticity with or without hypertonicity is naturally explained by an invasion of the pyramidal tracts somewhere in their long course.

Before even attempting to particularize, it should be understood that symptoms of the most varied sorts, many of them quite impossible of explanation, may occur which, as shown by post-mortem findings, must in some way be attributed to sclerotic patches of the sort under consideration. It is also a well-demonstrated fact that many lesions are discovered at autopsy which gave no recognized sign of their existence during life, notably in the brain stem involving the cranial nerve nuclei and fibers.

As before stated it is futile to attempt an exact determination of symptoms from lesions, or of lesions from symptoms, as is possible in other organic disorders, in which nerve elements are completely destroyed.

An attempt at correlation has been made by the earliest writers down to the present time. Charcot explained the ataxia and pain by invasion of the dorsal tracts, muscular atrophy by destruction of ventral horn cells, spasticity by involvement of the lateral tracts, nystagmus and difficulty of speech by lesions in the pons and oblongata, etc. Such

general statements are obviously unassailable. The difficulty arises in the more minute correlations.

Lesions found in the sacral region are regarded as responsible for the patient's sphincteric difficulties. The volitional tremor which next developed, is associated with patches in the superior cerebellar peduncle, red nucleus and optic thalamus. The nystagmus was associated with the periventricular and periaqueductal sclerosis. Patches in the cervical region are assumed to cause sudden numbness in the left arm, followed by rapid development of large areas in the pons, involving the eighth nerve and producing deafness, and in the facial nucleus, producing a facial paralysis. Later a patch involved the sixth nucleus, leading to diplopia from external rectus paralysis. Soon patches involved the twelfth nerve and nucleus, leading to protrusion of the tongue to one side with slight trouble with speech and swallowing; dimming of vision followed by total blindness the next morning was the result of the development of patches in the optic tracts and chiasm. The areas in the cord becoming more extensive, involved the lower motor neurons and resulted in muscular wasting and emaciation.

Brouwer believes that it may be possible to explain the chief symptoms of the disease through an appeal to evolutionary principles. The usual statement that the frequency of spastic conditions is due to an affection of the pyramidal tracts because these tracts are longer and therefore more exposed he regards as unsatisfactory. Furthermore, he does not agree with the generally accepted idea that sensory fibers are more resistant than motor fibers, hence the slight disturbance of sensibility.

To meet these various objections and to consider the symptoms from a unitary standpoint Brouwer appeals to the phylogeny of the nervous system. Reference is made to the following clinical examples in the attempt to establish his contention.

A patient with merely a slight paresis of the left facial nerve was almost totally unable to speak. The brain stem was much involved in the sclerotic process, also both the nuclei of the cranial nerves and their roots. Why, Brouwer asks, can such a patient not speak while showing practically

no changes in the function of the cranial nerves in general? In a second instance, he refers to loss of the abdominal reflexes. Why again is the nystagmus almost invariably horizontal? If due to foci in the oblongata, why are other cranial nerves not involved? In a case of practically complete transverse lesion of the thoracic cord the legs may be almost totally paralyzed, whereas the sensory disturbances are usually relatively slight. Finally, why is the temporal half of the optic disc paler than the nasal half, when apparently the entire nerve at some part of its course is sclerotic? A reconciliation of these difficulties is effected in the following manner:

Presupposing, as Brouwer believes justified, that multiple sclerosis is due to an infective agent of some sort, it is a fair assumption that the older parts of the nervous system have greater resistance to such agents than the phylogenetic and ontogenetic younger parts which naturally represent the higher, more developed functions. Reverting to the previous examples, the function of speech is a very late development, whereas the cranial nerve tracts are for the most part archaic. Hence, lesions, apparently affecting all this area in common, involve speech in a maximum degree because it represents a highly developed and late function. Again, the abdominal reflex only occurs in primates, hence it likewise is a late phylogenetic development and is therefore lost early because of its less resistance. The horizontal nystagmus is brought into relation with the fact that the side movement of the eyes in the horizontal plane is only present in higher mammals on account of the position of the eyes in the front of the head. Here again the same principle applies. That the disturbances of motility are greater and more frequent than those of sensibility is due to the fact that the pyramidal tracts are young both from the racial and individual standpoint. The cerebrocerebellar tracts in the pons are conspicuously developed in the higher mammals and particularly in man; therefore, a frequency of disturbed coordination since these late developed tracts are often involved in the sclerotic process. Finally, the much discussed temporal pallor of the disc (symptom of Uhthoff) finds its explanation in the imperfect crossing of the optic fibers in the mammalia, including man. Phylogenetically, the temporal half of the disc is the younger,

hence, according to the theory, it suffers more in the pathological process than does the nasal side. The well-recognized mental changes are naturally explainable on the same basis.

From the anatomical standpoint the (1) cortex, centrum ovale, (2) basal ganglia, (3) cerebellum, (4) optic system, (5) brain stem and cranial nerves, and (6) cord may with advantage be considered separately.

1. *Cortex.* Sclerotic areas in the cortex were slow of recognition. That very numerous plaques may occur throughout the cortex is no longer open to question. The relation of such alterations to the frequent mental changes in the disease may in general be accepted, although naturally it is quite impossible to associate definite symptoms of impairment with definite lesions. It is clear from many observations that, first, no exact correlation is possible between symptoms and lesions affecting the cortex and secondly, that the cortex may be extensively involved without corresponding mental disturbance.

2. *Basal Ganglia.* The connections of these nuclei with other portions of the brain are so complex and numerous that unless the lesions are sharply limited to the ganglia, deductions of value cannot be drawn. The characteristic rigidities, tremors (e.g., of the paralysis agitans type) and incoordinations due to lesions of this region of the brain are not conspicuous in the sclerotic syndrome. It is, however, not impossible that the ataxic tremor and alterations in tonicity may in part be due to involvement of the striatum or one of its divisions. Essentially the same may be said of the thalamus. The frequent occurrence of forced laughter and weeping, more frequent, but by no means peculiar to multiple sclerosis, finds, perhaps, its best explanation in thalamic or subthalamic lesions, but obviously this location cannot be its sole cause.

3. *Cerebellum.* The question as to how far lesions in the cerebellum affect the symptomatology of the disease is likewise involved in somewhat hopeless confusion, for the reason that, so far as I am aware, typical sclerotic patches limited to the cerebellum have not been described. If asynergia is the outstanding clinical feature of cerebellar disease, we may see in the dysmetria, tremor on volun-

tary movement, nystagmus, speech defects, without marked alterations in sensibility, a possible correlation between cerebellar lesions and symptoms. We are, however, in no way justified in assuming that these disturbances as seen in multiple sclerosis, are to be attributed only to the cerebellum and not to its connections with the brain stem and higher levels.

4. *Optic System.* We stand on slightly firmer ground in the attempt to correlate the clinical and pathological manifestations of the disease in the optic nerves, optic tracts and their cerebral connections.

The basis of our knowledge in this field was laid by Uhthoff in 1889, by an analysis of 100 cases with six autopsies in which the optic apparatus was particularly studied. In but one of these, no alteration was found in the nerve. In general he found what has since been amply confirmed, that with marked pathological changes in the nerve, the fundus may remain normal, that only slight ophthalmoscopic paling may occur, when the entire nerve is involved immediately behind the bulb, that under similar conditions the naked nerve fibers of the papilla and others are often relatively well preserved and there is no atrophy of the internal ganglionic cell layer.

Simple optic neuritis occurs in a certain proportion of all cases: 5 per cent in 100 cases (Uhthoff), once in 71 cases (Frank), 13 per cent in cases observed by Kampherstein. The occurrence of choked disc is a matter of interest. A case reported by Rosenfeld in which there was transient choking showed extensive lesions in the chiasm and nerve. Rosenfeld is of the opinion that sclerotic plaques directly behind the papilla may cause a true choking of the disc (*Stauungspapilla*), which may not be regarded as an expression of general intracranial pressure since a recurrence of severe brain symptoms does not primarily lead to a repetition of the choking. In general, as in other symptoms of the disease, these changes in the eyegrounds are apt to be transient and to give place either to recovery or slight atrophy. A rapid subsidence of swelling, apart from operation or other means for relief of pressure is characteristic of multiple sclerosis. Apparent total or partial atrophy of the

optic nerves is a much more frequent finding than choking of the disc. This condition is to be attributed to lesions in the nerve in close proximity to the papilla, but even this cannot be regarded as constant. For example, Eichhorst reports multiple sclerosis with optic atrophy in a mother and child. Wilbrand and Saenger found a large, clean-cut patch of sclerosis in an optic nerve, in which the vision and ophthalmoscopic appearance were both entirely normal. The general rule applies here as elsewhere, that so long as axones remain intact, function is not seriously interfered with. The varied disturbances of vision (52 of 71 cases in Frank's statistics): Sudden loss, unilateral loss, disturbance of vision as a first sign of the disease, changes in the fields, and color defects have been described by various observers. A correlation between these findings and the pathological changes is as unsatisfactory here as elsewhere.

The failure of secondary degeneration due to preservation of axones, accounts for the disparity between ophthalmoscopic appearances and alterations of the optic nerves. A predilection of the degenerative process for the papillomacular bundle may account for the frequent pallor of the temporal side of the disc.

5. *Brain Stem and Cranial Nerves.* The motor innervation of the eye (third, fourth and sixth nerves) is most variously affected and in the usual inconstant and erratic manner. Alterations in the size and reaction of the pupil, bilateral and unilateral have been described in bewildering variety and Argyll-Robertson pupil has been occasionally but very rarely observed—all without wholly adequate explanatory pathological alterations. The same is to be said of the external muscles. Spiller describes a case in which an "almost complete ophthalmoplegia" existed; an area of sclerosis was found post mortem, involving the nuclei of the third, fourth and sixth nerves and also the posterior longitudinal bundle. He observes, however, that the "cell bodies of the oculomotor nuclei are not very distinctly diseased."

The crura, pons and oblongata are very frequently and extensively invaded, but with relatively slight involvement of the cranial nerve innervation. As for example, in a

personally described case, the nuclei of all the nerves lay in sclerotic areas, with but slight disorder of function (Case II). Oppenheim is quoted as saying that he has continually found plaques in relation to the fifth nerve, without disturbance in the sensibility of the face. On the other hand, a persistent trigeminal neuralgia was also related by him to a sclerotic patch in the nerve root.

The facial and hypoglossal nerves may be slightly involved, the vagus and glossopharyngeal rarely. A satisfying correlation is rendered impossible here, as in the ocular innervation, by the possible involvement of higher levels, cortex or conduction paths. For example, the occasionally described weakness of the facial nerves is often of the cerebral type (Müller). The nerves of special sense, other than the optic nerve, in spite of lesions involving their origins or course, are seldom affected except in a minor degree.

6. *Cord.* Owing to the small transverse area and the length of the cord, the plaques of sclerosis almost inevitably invade all the tracts as well as the ventral horns, at some level. It is not surprising, therefore, that the greatest possible multiplicity of spinal symptoms should result. Ataxia, sensory disturbance of various sorts, sphincter disorder, sex difficulties, gait disturbance, tremor, muscular weakness, hypo- and hypertonicity, reflex alterations, occasional muscular atrophy and, in less degree, vasomotor defects may occur in various combinations.

The tendency to remissions is doubtless explained by a refunctioning of neurons, inhibited and not destroyed by the rapid development of the plaques, presumably under inflammatory conditions, much as the cranial nerves behave in epidemic encephalitis.

Interest centers particularly about the disturbances of motility in relation to predominant spastic conditions, about the relatively slight sensory defects, in spite of extensive lesions in sensory tracts, and about the rare lesions of the peripheral motor neurons sufficient to produce muscular atrophy. Spasticity is usually an early sign, as in a personal observation (Case IX), a case in which for a considerable period a spastic paraplegia dominated the clinical picture. More interesting and difficult of explanation are cases

such as described by Oppenheim, in which after the development of a well-defined symptom complex of multiple sclerosis, a spastic paraplegia later developed, confusing the diagnosis. Case XIII, abstracted below, at one period so closely simulated amyotrophic lateral sclerosis that for a time the diagnosis was in doubt, although earlier there had been no question of the existence of multiple sclerosis, which the autopsy confirmed.

Whatever the reason may be, the afferent tracts suffer much less symptomatically than the efferent corticospinal tract. General cutaneous sensibility is, as a rule, slightly affected, the sphincters more often and extensively, possibly because of the motor element in the reflex. (See case reports.) There are sparing descriptions of true muscular atrophy. Spiller, in the paper already alluded to, speaks of atrophy as very pronounced in the arms and legs, especially in the small hand muscles in one of his cases. A patch in a ventral horn of the lower lumbar region is pictured and alterations of nerve cell bodies were observed.

The original separation of multiple sclerosis into a spinal and a cerebral form has little to commend it owing to the fact that in the vast number of cases the degeneration is both cerebral and spinal.

A review of the widening clinical and pathological investigations, suggests the following classification. (1) A cerebral form in which the symptoms, chiefly of the sphincter control, point essentially toward the lower cord. (2) A cervical form to which Cassirer has drawn particular attention, and in which acute ataxia usually one-sided, stereognostic disturbances, slight spastic conditions and sensory disorders are characteristic. (3) A bulbar form with symptoms referring particularly to articulation, deglutition and other bulbar disturbances. (4) A pontine form involving particularly the facial and trigeminal nerves. (5) A cerebellar type characterized by asynergy. (6) A hemiplegic or hemiparetic form ushered in by apopleptiform attacks. (7) A form in which ocular disturbances occur early. (8) Spastic spinal conditions, including a disorder simulating amyotrophic lateral sclerosis, are predominant. These types present transition forms.

Personal Observations. The following cases are reported in abstract to illustrate some of the difficulties in correlation and diagnosis.

Case I. Schroeder. Transient ocular palsies, dimness of vision, tremor of head and hands, weakness of legs, attacks of falling, incontinence, final typical picture of multiple sclerosis. *Post mortem:* Complete transverse lesion of lower cord with extensive degeneration of other portions, ventral and dorsal root degeneration, especially of cauda equina, all cranial nerve nuclei in brain stem involved, brain not examined otherwise.

In this case there was essentially complete sclerosis of the optic nerves and tracts about the chiasm, although, in the clinical notes only dimness of vision is mentioned. One would also have expected more than transient ocular palsies. Tendency to fall, general weakness and incontinence find an explanation in the extensive cord lesions completely transverse at one point, but the symptoms are far less than one would have expected in so apparently complete interruption of tracts.

Case II. Schulz. Uncertainty of gait, disturbance of vision, vertigo, remission, weakness of legs, tremor, mental failure, change in speech, pain in legs, paresis of legs, slight facial involvement, paresis of external eye muscles with diplopia, nystagmus, pallor of the temporal side of the disc, irregular narrowing of fields especially for colors, active knee-jerks, sensibility for most part unaffected, finally paraplegia, incontinence, moderate dementia. *Post mortem:* Widespread lesions of brain and cord with involvement of the cauda equina, spinal roots and cerebellar cortex, cranial nerve nuclei invaded, in general with preservation of nerve cells; involvement of optic chiasm and optic nerves.

The incongruity between lesions and symptoms is well shown in this case. Disturbance of vision only is mentioned although again the chiasm is practically wholly invaded by sclerotic patches. Sensibility for the most part was unaffected in the presence of many lesions of sensory tracts, especially in the cord but also in the pons.

Case III. Gerngross. Examined by Oppenheim two days before death; scanning speech, probable complete bilateral external

ophthalmoplegia, normal fundus, contractures, tremor of intention type, active reflexes, for six months rectal and bladder incontinence, dementia. *Post mortem:* Widely distributed lesions in cord and brain, extensive cranial nerve involvement including the optic chiasm, many lesions in capsule, centrum ovale and cerebral and cerebellar cortex.*

Correlations in this case are of small value on account of the fact that the available physical examination was made so short a time before death. As given, the symptoms could not properly be accounted for by the lesions found, notably the complete external ophthalmoplegia.

Case IV. F. N. D. Lameness and numbness of right leg extending to other side, improvement; articulation and vision disturbed, slight difficulty in swallowing, some ataxia, active knee-jerks, disturbance of sensation in the legs, fundus normal, again improvement; later irregularity of reflexes, crossed paralysis, spasticity, no intention tremor, nystagmus or characteristic speech defect. *Post mortem:* Predominant lesions of the spinal cord, nerve cells not markedly involved. This case was atypical throughout its course.

Case V. M. M. Emotional, sensitive to noises, speech defect, headache, staggering gait, numbness of right hand, paresis of right seventh nerve and of the left sixth, knee-jerks increased, nystagmus, no choking of discs, various disorders of sensibility, paralysis increasing up to death. *Post mortem:* Sclerotic areas throughout brain stem, no record of cerebral hemispheres or of the cord, doubtful case during life particularly because of well-marked sensory disturbances.

Case VI. E. H. Active reflexes with double Babinski, gait weak and spastic, some numbness of the right, change of temperament, inequality of pupils, pain in back and legs, muscular spasm, slow light reaction, incontinence. *Post mortem:* One large lesion found in the white matter of the brain, other smaller ones, numerous sclerotic areas in the cord, diagnosis of multiple sclerosis not made during life. The case suggested rather a diffuse combined degeneration of the Putnam-Dana type.

Case VII. E. F. Disturbed sensation in legs, pain, difficulty in walking, knee-jerks active, double Babinski, some ataxia of arms and legs, tremor of hand, atypical scanning speech, nystagmus,

* Cases I, II and III reported in *Deutsche Ztschr. f. Nervenh.*, 1894, v. 1.

increasing difficulty in walking, legs extended and spastic, no involvement of cranial nerves, emotional, abdominal reflex absent, slight facial paralysis speech becoming unintelligible. *Post mortem:* General distribution of plaques throughout brain and cord with marked changes in nerve roots.

Only a few sections were made from this case. So far as they are available for study the atypical character of the symptoms is somewhat adequately explained by the relative fewness of the sclerotic patches in the cord and brain.

Case VIII. C. F. R. First symptom, poor vision, staggering gait, pain, some lead found in the urine, later urinary retention, right arm weaker than the left, no objective disorder of sensation, active reflexes, cremaster and abdominal reflexes lacking, considerable unsteadiness of station, fundus normal at first examination, later suggestion of atrophy, defect of vision of left eye, syphilis as well as lead suspected. *Post mortem:* Multiple sclerotic lesions. Detailed examination not made by me.

Typical course with typical lesions excepting that the cord appears less involved than the brain and the spastic paraplegia dominating the clinical picture for a considerable time finds no adequate explanation.

Case IX. M. S. Weakness of legs, temporary but recurring facial paresis, special weakness developed in the right arm and leg. For a time a spastic paraplegia dominated the picture, slight ataxia, general weakness, reflexes active, Babinski, slight nystagmus, speech slow and scanning, spasticity of legs without sensory disorder, increasing difficulty in walking, later extreme volitional tremor, typical scanning speech, nystagmoid movements, no continued paralysis. Pallor of temporal sides of discs, tremor of the diaphragm suggesting an intention type shortly before death. *Post mortem:* Cerebrospinal sclerosis, general and extensive.*

Case X. A. E. H. At eighteen dragging of left foot, several falls. At thirty reeling gait with tendency to fall, examined by Drs. J. J. Putnam and M. A. Starr. Speech defect at thirty-seven, obliged to use crutches; failing judgment, wheel chair at forty-three. Disease progressive with temporary improvement. For ten years unable to focus, external squint, irregularity of pupils, conversation unintelligent, mental defect well marked, no definite

* Cases IV–IX reported in *J. Nerv. & Ment. Dis.*, 1906, xxxiii, 361.

alteration in reflexes but tendency toward exaggeration, final difficulty in swallowing and extreme mental deterioration. *Post mortem:* Disseminated lesions of hemispheres, walls of the ventricles, pons and, to a lesser degree, in the cord.

The brain in this case was spattered with lesions, the cortex included; wherein may be found a somewhat unsatisfactory explanation of the pronounced mental changes resulting in dementia.

Case XI. J. A. O. For six years pain in the right calf, later in calf and ankle extending to the left side, walking became impossible, slow pupillary reaction, no knee-jerk (due probably to contractures), ankle clonus and Babinski present, sphincter involvement, fundus negative, Wassermann negative, no mention made of tremor, nystagmus or speech defect. Diagnosis during life, *transverse myelitis.*

First sacral, fourth and fifth lumbar pairs of dorsal roots cut for relief of pain and with the hope of relieving the high degree of spastic paraplegia. *Post mortem:* Sclerotic patches were found in the crura, pons, oblongata and conspicuously in the cord. In the crura there were two small areas of degeneration. In the quadrigeminal region, a well-marked area in the pyramidal tract, one side; in the upper oblongata one pyramidal tract markedly involved, in the lower both pyramidal tracts. Again, in the cervical cord the predominant lesions were in the pyramidal tracts but here the sensory areas were extensively invaded as well. In the dorsal region extensive degenerations involving both motor and sensory tracts; in the lumbar region the plaques were not so pronounced.

This case is to a certain extent but not adequately explained by the lesions. At no time was a definite diagnosis of multiple sclerosis entertained. The symptoms pointed to a fairly sharp and circumscribed transverse lesion of the cord which did not exist. The marked spasticity with tendency to contracture is doubtless explained by the definite involvement of the pyramidal tracts; the extreme pain is altogether unusual though not undescribed (Nonne), and might be explained by involvement of dorsal nerve roots which, however, was not demonstrated microscopically. The relatively slight sensory disturbance apart from pain is noteworthy in view of the lesions found. The case in general is of rather striking

interest as demonstrating the great difficulty of correct diagnosis during life.

Case XII. C. B. Numbness and weakness of legs, girdling sensation, poor accommodation response in the left eye, tremor, absent abdominal reflex, exaggerated knee-jerks with double ankle clonus and Babinski, ataxia of arms, marked Romberg sign, spastic gait. In general, signs largely confined to the leg. Ayer, double puncture, negative, gold sol, paretic zone. Tumor of cord suspected during life; laminectomy and exposure of the cord showed various patches, presumably multiple sclerosis.

Case XIII.* A. C. Onset with paralysis of legs, loss of sphincteric control and intense headache. Pupils unequal and irregular, right hand grasp stronger than left, knee-jerks exaggerated, double clonus and Babinski, Romberg sign, persistent paralysis of legs, disturbance of pain sense, increasing incontinence, scanning speech, vertical nystagmus, slight volitional tremor, emotional, probable left astereognosis, marked muscular atrophy especially of left arm and hand with conspicuous exaggeration of reflexes and spasticity of legs. Diagnosis of multiple sclerosis was repeatedly made during the earlier course of the disease; toward the end the possibility of an amyotrophic multiple sclerosis was strongly entertained. *Post mortem:* Typical lesions of multiple sclerosis, special interest centering in the lesions of the cervical gray matter with reference to the pronounced muscular atrophy of the hand muscles. Microscopic examination of ventral horn cells in the cervical region showed certain definite changes of degenerative character, though by no means so extensive as one would find in well-advanced progressive muscular atrophy of the spinal type.

Case XIV. F. L. W. Onset with progressive weakness of the legs, associated with numbness and paresthesiae, roughly up to the waist. Slight failure of vision, vertigo and tinnitus; nystagmus, both lateral and horizontal, right pupil larger than the left. Abdominal reflex bilaterally lost, loss of sense of position in legs. Increasing and progressive weakness of the legs. Deep reflexes all increased but more in legs than arms; ankle and patellar clonus, positive Babinski and Oppenheim response on both sides. *Post mortem:* Multiple sclerotic lesions of the cord with a small focus of softening in the thoracic region. The brain was not examined.

In this case the following possible diagnoses were made during life: Tumor of the cord, combined sclerosis, transverse

* I am indebted to Dr. Hugo Mella for the clinical history and preparation of sections in this case.

myelitis, and, as "a very distant possibility," multiple sclerosis. Tumor was thought to be so probable that a laminectomy was done, naturally with negative results. More importance should have been attached to the progressive weakness, the visual disturbances, the absent abdominal reflexes and to the gold sol reaction which was in the luetic zone, in the absence of all other findings in the fluid, suggestive of syphilis.

This group of cases illustrates in concrete form the difficulties of diagnosis and the impossibility of accurately correlating the clinical symptoms with post-mortem findings. A cursory analysis emphasizes the following points: A definite ante-mortem diagnosis was consistently made in only 6 cases and one of these was doubtful during the latter part of life. The lesions stood in no predictable relation to the signs and symptoms during life, notably those of the oblongata and pons involving cranial nerves. Several of the cases with generally disseminated lesions, strongly suggested sharply localized defects, for example, Case XI, transverse myelitis, Cases XII and XIV, tumor of cord, Case XIII, in late stages amyotrophic lateral sclerosis. This is wholly in accord with the observations of many others and requires no further comment. It is evident that exact correlations cannot be made.

Conclusions. In summarizing this involved question the following conclusions appear to be warranted by the facts as yet at our disposal. As in other structural diseases of the nervous system a general correlation may be made between lesions in certain localities and symptoms due to such lesions. It rarely happens that symptoms occur without any discoverable lesion. The degree of disturbed function depends upon the age of the lesion, since the older the lesion the greater the destruction of nerve elements. The most satisfactory correlations have been made in connection with vision and the optic nerves and tracts. Sensory, motor or mental disorder may certainly be attributed to lesions occurring in the areas of the central nervous system disturbing these functions, but a precise determination of lesions from symptoms or of symptoms from lesions is not possible. This is due to the following causes: First, to the peculiar

type of degeneration in the disease, particularly the long persistence of axones and the resistance of cells, and secondly, to the multiplicity of lesions which confuse the clinical picture. For instance, one is not justified in attributing mental changes to cortex lesions, when association tracts and deeper structures are also involved, nor can we say that ocular or other palsies are due to nuclear lesions when the cortical controlling areas or the connecting pathways are likewise involved. A wholly satisfying explanation of the so-called cardinal symptoms of the disease is not yet forthcoming. It is, however, fair to assume that the loss of myelin and the localization of lesions in coordinating areas are both, in part, responsible for the characteristic volitional tremor in its manifestation as nystagmus, speech defect and general ataxic tremor. Apart from these somewhat unique disturbances, the other signs and symptoms of the disease, which are coextensive with the symptomatology of the nervous system in general, find their explanation in the multiplicity of the lesions, their localization and their degree of destructiveness. An attempt to draw accurate physiological deductions is usually fallacious, and always misleading.

The following questions submitted to Dr. Taylor before the Commission, together with the answers to them, are here reported verbatim.

Dr. Sachs: What has your own experience been regarding the frequency of mental changes in multiple sclerosis? Of course, the percentage that we have found is in keeping with our records and from my own personal knowledge, I must confess that I was rather startled to hear the high percentage that someone else claimed—almost 100 per cent.

Dr. Taylor: I think it was one of the older authors. I am sorry to say I cannot answer Dr. Sachs' question from my personal experience, particularly because I have not been able to observe many of these cases with the care with which I should like to observe them, and as for giving any statistical data on that, I am quite unable to. I think, however, the disparity arises in the interpretation of mental symptoms. Any slight changes in character, any euphoria or anything of that sort, I take it, has been regarded by authors as mental changes. Excluding the so-called forced

laughter and forced weeping, the lability of temper in these patients is regarded by these authors, I think, as a mental change. Doubtless you took the term "mental" in a more restrictive sense. That I think is a matter depending upon the use of words.

Dr. Sachs: May I ask Dr. Taylor, whose knowledge of histological changes and so on is great, whether he has discovered any evidence of syphilitic vascular involvement in any of his cases of multiple sclerosis? It is a very important point, I believe, if it can be established, in view of the claim that was made, for instance, by Marie and his followers as to the intimate connection between the two diseases. I should consider the evidence of syphilitic vascular changes in the immediate vicinity of sclerotic patches or in some relation to them, as a very important point of evidence, and I would ask Dr. Taylor whether he recalls anything of the sort.

Dr. Taylor: I have not, but there again I think my opinion is worth practically nothing, because I have not personally done very much histological work of late years. When I did work on the subject, before this matter of the relation of syphilis was brought into prominence, I did not find any such relationship; in fact, I did not at that time feel that the blood-vessels had any distinct bearing upon the degeneration. It seemed to me incredible, and it does still, to explain such lesions as we see in those areas as due to a vascular change, and a vascular change alone. Some other element must enter into the situation. However, I cannot answer definitely Dr. Sachs' question.

Dr. Barker: Do you think that the character of the lesion, the sharp circumscription of the lesion, is consistent with the idea of an inflammatory process or an ordinary toxic process with a diffusible toxin?

Dr. Taylor: It does not seem to me that this can be explained by an ordinary inflammatory process starting from the blood-vessels. A diffusible toxin would seem to me a far more plausible explanation, and I think I at one time expressed that idea some years ago, as a possibility. In one of the sections of one of those pictures of sclerosis, there is a perfectly distinct degeneration and then an area of more vague degeneration surrounding it, which seems to me inconceivable to explain on the basis of an ordinary inflammatory process as we understand inflammation.

Dr. Tilney: Do you think there is any general statement warranted at present as to selective histological localization of the lesion? You spoke so much of the effect on the myelin. Is it your judgment that the lesion affects the medullary substance more than the gray matter, that it perhaps has its origin there and spreads out subsequently?

Dr. Taylor: I believe that it must be a selective lesion, from a pathological standpoint, inasmuch as we know of no other condition in which the myelin is involved to this extent. Of course, there are other conditions such as the periaxial neuritis, for example, and conditions of that sort, in which the myelin suffers, but that it suffers to the degree that it does in this disease, with the slight involvement of the axone, seems to me rather improbable.

In the second place, regarding the extent of the process in the gray or white matter, I have never been able to convince myself that the gray was less involved than the white matter; it seemed to me, from studying these innumerable lesions, that the process, so far as we could determine, played its part perfectly irrespective of gray and white, and that the apparent difference lies in the fact that the gray matter is less extensive than the white, on the whole, throughout the central nervous system. Those are matters which come without the scope of my particular paper, and I suppose will be absolutely elucidated this afternoon.

Dr. Hunt: Do you correlate the intention tremor, which is so striking a symptom of the disease, with any special system in the central nervous mechanism?

Dr. Taylor: My feeling about that is that such a definite correlation is not possible. It seems to me, following Dawson and many others in this regard, that the most we can say is that if it has a definite localization, it is due to a disturbance somewhere between the cerebellum and the cortex, somewhere in that whole coordinating mechanism involving the thalamus and connecting the paths between the thalamus and the cerebellum. I do not believe we are justified in maintaining that it is due to a lesion of any one portion of that large tract and I cannot help but feel again, contrary to the best opinion perhaps at the present time, that the loss of myelin has something to do with that peculiar coordination—just how I do not know, but it would seem so, inasmuch as it does not occur to the same degree in any other form of the same disease.

Dr. Prince: I would like to ask two questions. First, have you any theory to explain the remission of the disease through the character of the lesion? Second, the absence of secondary degeneration ascending and descending, is that to be explained entirely by the preservation of the axones, or do you get these secondary degenerations after the process has gone on a certain length of time with the destruction of the axones?

Dr. Taylor: The question of remissions is, I suppose, best explained on the basis of the newer pathological anatomy, namely, that it is in some sense possibly an inflammatory process and as

such, these various processes or foci, as in encephalitis, for example, occurring at one or another part of the nervous system, result in immediate effects, of course, as any acute process will. When the lesion grows older, and there is a certain restoration of function, and the shock effect has worn off, then I can conceive that the whole clinical picture would definitely improve. Now, if that takes place, conceivably in a large number of these areas, I can conceive of a distinct improvement in the clinical symptoms. If it is true that this disease is due in some sense to a toxin (using that term in a very unscientific fashion), it is possible that we may have new accessions of this poisonous material, which lead to these acute exacerbations of pathological lesions thus produce an exacerbation of symptoms.

The other question as to the pathological degeneration is explained by the persistence of axones and in the late lesion we may have secondary degenerations. The degree of degeneration in these lesions, as seen in Fuller's case, I think cannot possibly be explained by the sclerotic foci.

Dr. Patrick: Apropos of the myelin lesion, I should like to ask if you have not seen perfectly well-developed intention tremor following lethargic encephalitis.

Dr. Taylor: I do not think I personally have. I have seen all sorts of other tremors indicative of basal ganglia lesions, possibly, but I do not recall having seen a case of intention tremor.

Dr. Strauss: I would like to ask, since I do not think it has been mentioned this morning, whether you have encountered the difficulty, in cases of possible spinal multiple sclerosis, of differentiating from spinal cord neoplasms?

Dr. Taylor: There are at least 2 cases of the series of 14 (and I am not sure in but 3—they are detailed in the paper), in which spinal cord neoplasm was so seriously entertained that operation was done, revealing, as I stated briefly, the fact that many sclerotic lesions alone accounted for the lesions. In those cases, in the light of the post-mortem examination, certain slight symptoms should have created more suspicion than was aroused in the actual diagnosis.

An Investigation of the Axis Cylinder in Its Relation to Multiple Sclerosis

Joshua H. Leiner, M. D.

It can no longer be doubted that in multiple sclerosis either in the acute or chronic form, the axis-cylinder suffers a distinct injury.

On the other hand, no one will be inclined to doubt that in the presence of fully developed sclerotic patches, despite the greatly advanced disintegration of the medullary substance, both in recent and old plaques, there is still found existing preserved axis-cylinders.

However, a series of questions referable to the axis-cylinder are still unexplained, which probably, through the application of modern methods of investigation, will in time be cleared up.

An attempt is, therefore, made to solve a number of questions concerning the axis-cylinder by applying the method adopted by Jakob (analine blue and gold orange method according to Mallory), which allows of a distinct differentiation between the axis-cylinder, the medullary sheath and the glia in one and the same section. As a matter of course, we have also examined sections stained by the Bielschowsky method by way of comparison, and also sections arising from acute processes as well as those of an outspoken and pronounced sclerotic character.

The changes the axis-cylinder undergoes as a result of multiple sclerosis are approximately the same as described by Marburg as occurring in the acute types of this disease.

The outstanding features are thickenings, globular distentions, vacuolization, disintegration and further the appearance of thin threads, in the older sclerotic areas. One sees occasionally, the presence of separated fibrillae pushed up or scattered along the periphery.

In observing these changes one cannot help being impressed and wonder at the absence of secondary degeneration in axis-cylinders showing such serious deterioration, and at the same time attempt to account for it. It is possible that we are confronted here with certain edemas (which will be gone into more fully later), that are reversible in nature to a certain extent in the acute cases and to a less degree in the chronic types.

It is known that Marburg has drawn a parallel between the changes observed in the medullary sheath in multiple sclerosis and that found in the periaxial neuritis, i.e., the Gombault-Stransky type. According to him, the medullary

sheath breaks up first, whilst the axis-cylinders remain comparatively uninjured. This type of medullary disintegration unknown heretofore to occur in the central nervous system, has since been demonstrated by Shimazono to occur in animals who were subjected to experimental lead poisoning. In Shimazono's sections, however, one is impressed with the fact that the axis-cylinder is not distended and edematous as observed in multiple sclerosis, but rather broken up into rows of granules, having previously become narrower and thinned out.

Kimura in his investigation into the degenerative and regenerative processes of the peripheral nervous system, reports similarly, and he further greatly restricts the term periaxial degeneration in peripheral nerve involvement. This investigator also believes that primarily the axis-cylinder is mostly injured in the neuritides. It is true he does not preclude the destruction of the medullary sheath round the still existing axis-cylinder, yet he assumes, that to bring about the former, there must be a serious lesion of the peripheral nerve. He adds further, that in nerves in which the medullary substance has already broken up into clumps, no well-preserved axis-cylinder is to be found.

Since the axis-cylinder perishes before the medullary sheath is entirely broken up, we must assume that a long smooth axis-cylinder when seen in the field, is formed out of vacuolated fibers, at least as far as the peripheral nerves are concerned. These facts established with regard to the peripheral nerve would seem to contradict the existence of a periaxial neuritis type of reaction.

Siemerling and Raecke maintain in their comprehensive studies, which forms a compilation of all the essential points referring to the axis-cylinder, that the lesion of the nerve is primarily manifested in the axis-cylinder. They believe the process to originate in the vascular system, an hypothesis actually adopted by Fraenkel and Jakob, having for their reference the smallest areas that are just developing. A process originating in the vascular system and chiefly affecting the medullary sheath, has been known for some time. This manifests itself particularly in cases of pernicious anemia, a process the pathological character of which has so

far been by no means ascertained. It is attended by a complete destruction of all the nerve fibers within a limited area.

Shimazono, as well as more recently Wohlwill, has shown in these cases of pernicious anemia that the axis-cylinder is primarily injured and an enormous distention of the axis-cylinder takes place. The medullary sheaths are at first only passively stretched. The glia then begins to proliferate by way of reaction and seemingly compresses the axis-cylinder, which it eventually absorbs after its disintegration,

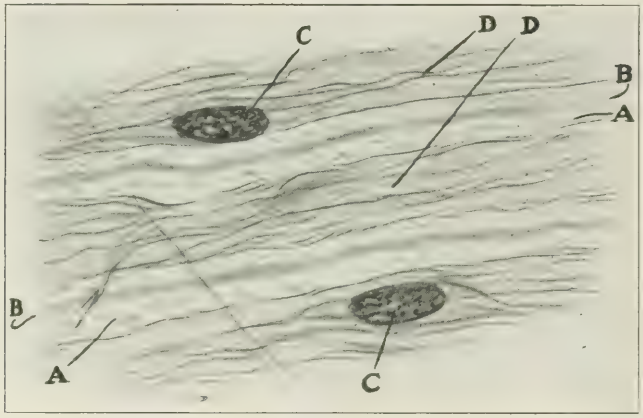

Fig. 1. A well advanced stage of myelin disintegration; glia cells with pigment. *A*, myelin fragments; *B*, axis cylinders fairly uniform, although myelin disintegration is advanced; *C*, glia cells with pigment, broken down lipoids; *D*, glia fibers. Mallory stain, Jakob modification; oil immersion; ocular 8. (*Arch. Neurol. and Psychiat.*)

whilst the medullary sheath disintegrates in its turn as pointed out by Wohlwill, not into large clumps, but into small particles. At the same time a narrow line of medullary sheath attaches itself to the heavily degenerated axis-cylinder.

We have, therefore, two diametrically distinct processes affecting the nerves. The one alleged to begin in the axis-cylinder, the other in the medullary sheath.

The existence of the latter cannot possibly be doubted if we examine the slides of multiple sclerosis in longitudinal sections beyond the affected areas. One may actually see the axis-cylinder becoming uncovered and then recovered again at the far end of the small area.

The line of thought pursued by Kimura is hardly justifiable. He assumes a serious lesion to exist remotely in the correlative nerve.

There is only one difference apparently distinguishing experimental neuritis from the periaxial type accompanying multiple sclerosis, i.e., the comparative slenderness of the axone and the granular disintegration occurring overwhelmingly in the former, while in the latter condition the presence mostly of swellings and distention.

The first question of interest for us would seem to be whether the axis-cylinder is primarily injured and the medullary sheath secondarily, or vice versa. It is indeed rather difficult to draw such conclusions from histological pictures alone, since indications as to time, the chronological development of the process is not easily to be inferred from the local phenomena displayed under the microscope.

If we go through several of Jakob's slides, making due allowance for the above-mentioned difficulty, we see that in the advanced stages of the majority of the cases, the medullary sheath is already completely destroyed, and yet there is no denying the fact that when one studies the slides closely that one sees remnants of the medullary sheath preserved a long time, and distinctly visible a yellow-tinted margin lying along the periphery of the axis-cylinder. Occasionally, even a nerve will be discovered possessing, as described by Wohlwill in cases of pernicious anemia, an inflated axis-cylinder and a relatively thin but as yet intact medullary sheath. Of course, one can never be prepared to state that there may be a region close to the intact medullary sheath, where disintegration has already set in.

In the majority of cases, however, one thing is certain, that the lesion of the medullary sheath is more serious than that of the axis-cylinder. Regarding the number of perished axis-cylinders, it cannot be compared to that existing in myelitis or encephalitic diseased areas.

Both in the acute cases as well as in the chronic types, we can see what Doinikow has drawn and illustrated in such an exquisite manner, and which is also to be gleaned from the writings of Marinesco and Minea—the button or globe-

shaped inflations, partly forming a sort of club at the ends, partly resembling a globular distention along the axones.

This then leads up to a second question to be settled, one that has been diligently discussed, i.e., with reference to the question of regeneration of the axis-cylinder.

There is little to add to the statements or the carefully attempted conclusions drawn by Doinikow—whether degen-

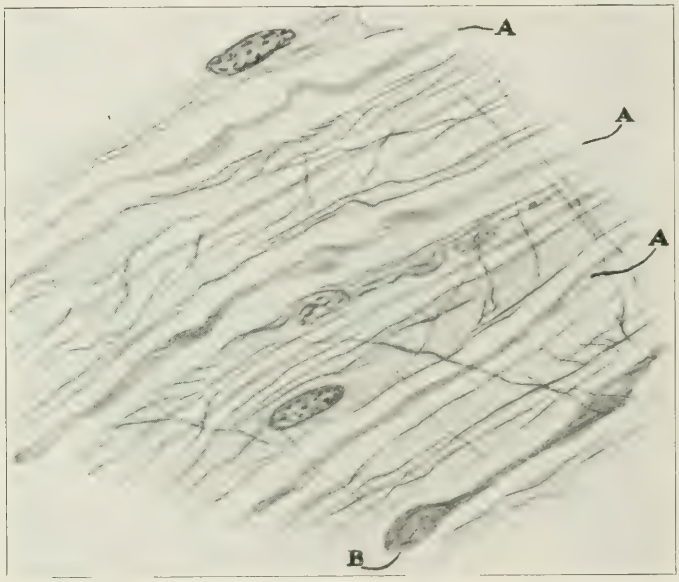

Fig. 2. The myelin has entirely disappeared. The axis cylinders are surrounded by glia fibers. *A*, Naked axis cylinders, uniform caliber gone, distorted in shape and showing vacuolization; *B*, an inflated end bulb type. Mallory stain, Jakob modification; oil immersion; ocular 8. (*Arch. Neurol. and Psychiat.*)

erative or regenerative phenomena cause or are conducive to the formation of these end-globules.

However, there has been demonstrated in the Vienna Neurological Institute, by Miyake, that only one day following a complete section of the spinal cord, these spherical bodies and club inflations were observed on the axis-cylinders, i.e., at a period of time when regeneration can hardly be thought of. Consequently, it is impossible to draw any inferences or conclusions pointing to the above phenom-

ena, as representative of regeneration, particularly when we know that it is impossible to ascertain the exact time of origin of the appearance of a particular acute process. However, this can be said, that if we observe thread-like processes or fibrillae spurting out of the globular distentions, we may take this as an attempted indication of the beginning of regeneration. This, however, can by no means sufficiently account for the preservation, in many areas, of a rather considerable number of naked axis-cylinders, though even in an altered form, still capable of conduction however, owing to the absence of the manifestations of secondary degeneration. Again, we cannot agree with Kimura's view of judging a long smooth vacuolated axis-cylinder always as having been newly formed. On the other hand, it would appear that the apparently newly formed axones are by no means unchanged. Some are thicker, while others are thinner than those wrapped in the medullary sheath. They have been so described by nearly all authors who have dealt with this problem.

We can, therefore, only assume that the lesion of the axis-cylinder during this process need not be such a profound one as to lead to the destruction of the axis-cylinder in all cases, but that we have to deal here with a process which is, to say the least, different from the one consequent upon pernicious anemia, since in the former condition the axis-cylinder does become edematous, it is true, and even falls into decay if the edema be carried too far, but is preserved in a greater number of cases when the swelling subsides. The preservation and intactness of the fibrillae, which one can opportunely ascertain in the axis-cylinder, would seem to confirm this view. On the other hand, we can by no means speak of regeneration of the medullary sheath. One can hardly interpret the medullary shadows (*Markschattenherde*) of Schlesinger, as significant in this sense. However, the process of disintegration of the medullary sheath, along with the comparative intactness and preservation of the axis-cylinder, must be looked upon and regarded as a specific characteristic of multiple sclerosis.

We may find an explanation for the peculiar relationship between the axis-cylinder and the medullary sheath in the

work lately done by Spiegel of Vienna, at the Neurological Institute. He has succeeded in proving by his experimental researches, that every lesion of the medullary sheath must be followed by one in the axis-cylinder —on the basis of physico-chemical reasons.

The remarkable point about the facts revealed by the polarization microscope is, however, that the edematous nerve may return to its normal condition with regard both to anatomical structure and function, and the edema subside, providing the noxious influence has ceased to exist. The inference to be drawn, therefore, is, that an injured medullary sheath will, of course, if the noxious influence continues, occasion a lesion of the axis-cylinder in the shape of swelling, and it will depend solely on the degree to which the latter has developed whether the lesion will prove deleterious or whether, after the cessation of the toxic product, the normal state will be attained again. Each swelling of the medullary sheath or its decomposition is followed, therefore, by an edema of the axis-cylinder and eventually by its destruction, or vice versa. In the light of the above work, we must, therefore, assume that as far as pernicious anemia is concerned, we have toxins that injure primarily the axis-cylinder, which is so convincingly described by Wohlwill. Again the disintegration of the medullary sheath in the course of these diseases is essentially different. In pernicious anemia the disintegration takes the shape of small granules, while in multiple sclerosis we find course lumps. This observation on the decomposition of the medullary sheath may give us perhaps a method of differentiating between the primary disintegration of the medullary sheath and the secondary type-lesion of the axis-cylinder. In any event, these two processes cannot be paralleled quantitatively, so great is the difference.

As to the toxic agent, we cannot assume that its varying strength causes at times one type of lesion and at another time a different process, but must attribute these pathological processes to a difference in type of toxin.

Aside from the question of toxic intensity or type of toxin, one must bear in mind certain well-differentiated elements and tissues of the central nervous system and their individual-

ized property of reaction. As an illustration one need only remember the dissimilar reaction of the spinal cord towards cocaine, and of strychnine, as demonstrated by Sano. He has shown that the spinal cord is detoxicated of the former through the media of the anterior cornu, and the latter through the posterior horn. If such considerable chemical differences exist in the gray substance, we must suppose them evident also in the more differentiated structure of the medullary sheath and the axis-cylinder. There are evidently toxins, either endogenous or infectious, that at one time evince a special affinity for the gray and at other times for the white substance. It cannot be doubted that the toxin or the infection of multiple sclerosis injures and shows preeminently a selective action on the nerve fibers.

If we finally turn to the reaction of the glia in the vicinity of the neuron in multiple sclerosis, we find that the neuroglia is comparatively free from serious involvement. The appearance of an excessive fibrillar growth is its most striking feature. We see the axis-cylinder becoming surrounded by a distinct visible sheath of glia, a sort of envelop, and a delicate network appearing more distinctly and densely between the glia cover of the medullary sheath and that of the axis-cylinder. That which is observed in rough outline in the plaques as a whole, is reproduced in each individual fiber. It would seem quite possible that the above-described reaction of the glia would form a kind of protective barrier against further aggression and damage towards the denuded axis-cylinder—a substitute for the lost medullary sheath. A glia fibril genesis seems to be a definite picture in this process, and it exceeds by far the cellular element proliferation of the glia.

In conclusion one may state the following:

1. That the axis-cylinder suffers a lesion which may lead to its destruction.

2. That in a great part of the time the axis-cylinders survive the lesion, and that the primary edema is followed by a subsidence of the same.

3. That our sections have proved further that the disintegration of the medullary sheath is in every respect more complete than that of the axis-cylinder and that it may be

found completely destroyed even when there are comparatively well-preserved axis-cylinders present.

4. That in isolated instances the medullary sheath is preserved at least in part, in the shape of a ring round the axis-cylinder.

5. That for an explanation of the lesion affecting the axis-cylinder, we may adduce Spiegel's conception, that every decomposition or disintegration of the medullary sheath, is accompanied by a simultaneous edema of the axis-cylinder, evoked by chemicophysical processes.

6. That these edemas are reversible, not only pertaining to anatomical configuration but also to function.

7. That this conception may explain the clinical fact, that despite the presence histologically of a serious lesion, the function was found preserved, and probably a further explanation is furnished by the phenomena of the glia, forming a dense protective cover round the axis-cylinder in the earlier stages of the disease, taking the place in part of the disintegrated medullary sheath.

The following questions submitted to Dr. Leiner before the Commission, together with the answers to them, are here reported verbatim.

Dr. Spiller: So far as I know, the very first evidence of a change affecting the medullary sheath of the peripheral nerves was obtained by Gombault in his peripheral neuritis, to which his name has always been attached. I had been inclined to believe that that was simply a certain stage in the neuritis; that if sections had been delayed longer and had been taken in a more advanced stage of the disease, that the axis-cylinders would have been more affected than Gombault found in his disease.

I should like to ask whether it is not believed that while the medullary sheaths in multiple sclerosis are affected before the axis-cylinder, if, after all, that is anything peculiar? Are not the medullary sheaths in most conditions affected before the axis-cylinders? The latter are certainly more resistant.

Is there anything, therefore, in any way particularly characteristic of multiple sclerosis in the change in the medullary sheath?

As for the glia, it is undoubtedly true that it varies very greatly (does it not?) according to the time when you examine the multiple sclerosis case. Therefore, after all, are not the findings due more

to the period at which the examination is made, than to anything that is strictly pathognomonic of multiple sclerosis?

Dr. Leiner: I agree with Dr. Spiller in toto. Multiple sclerosis, as viewed, must be divided both histologically and clinically into different stages. We can assume them to be acute; then a period of acute subacute; then a period of subacute chronic, and then entirely chronic; and that stage you will find associated with the remissions. When the remission ends and the exacerbation begins, you again will go through the acute, subacute, and chronic stages. This has been demonstrated. One can see old plaques and new plaques forming one directly alongside the other.

In regard to the toxin: Unquestionably if the attack of the toxin, whatever it may be, endogenous or exogenous, is very strong upon the medullary sheath, that will determine whether the disintegration of the medullary sheath will go on to an involvement of the axis-cylinder.

Dr. Taylor: Do you regard the process of multiple sclerosis as primarily inflammatory or primarily degenerative?

Dr. Leiner: This is very difficult to say, from histological pictures alone, but there has been an attempt made of dividing multiple sclerosis into different types, the so-called "stormy" type and the so-called glia type, the chronic type, which is akin to syringomyelic involvement of the glia. I think, the subject rests here, and the query is: Have we really got 2 types of multiple sclerosis?

I think, if we want to approach the subject, we should divide the cases into those of an acute type and those of a chronic type. I have tried unsuccessfully to find spirochaeta pallida in connection with acute types, with the silver stain.

Conclusions of the Commission Concerning the Pathology of Multiple Sclerosis

The papers presented to the Commission, and the discussion which followed their presentation, brought into prominence three questions. First, is the pathological process in multiple sclerosis of an inflammatory or degenerative nature? Secondly, is multiple sclerosis in the latest stages a sequel of an acute inflammatory process? Lastly, is the disease due to a microorganism?

The conclusion reached by Hassin from his careful study of a number of cases of well-developed multiple sclerosis was that the process was conclusively degenerative, and due

to some unknown toxin, probably endotoxin. Spiller in his presentation showed preparations of cases which he regarded as acute multiple sclerosis, in which there was distinct evidence of inflammatory change. He took exception to the view that the process is primarily degenerative, but thought the appearance shown in cases of multiple sclerosis of long duration was the result of a previous inflammatory change of an acute nature.

The Commission finds it extremely difficult to decide conclusively between these two divergent views. This decision rests upon, first, does there really exist a clinical and pathological entity such as acute multiple sclerosis? Second, is it certain that the cases reported in the literature under this diagnosis are not cases either of encephalitis or lues? If the Commission could decide this question in the affirmative, it would then have to admit that there may be two forms of multiple sclerosis, one which commences as an acute inflammatory process and later develops an histology the character of which is purely degenerative, and another which never presents any of the characteristics of inflammation, but in which the process is degenerative from the onset and throughout its continuance. From the evidence presented, the Commission is unable to decide these questions. Further research and investigation along these lines will be necessary before a satisfactory conclusion can be reached.

The work of Teague in searching for a microorganism, especially a spirochete, in cases of multiple sclerosis, has yielded a negative result. He was unable to confirm the findings of European observers in this regard. The Commission thinks that a negative result, while not as valuable as a positive one, nevertheless, in view of the histological character of the pathological process of multiple sclerosis, must induce a cautious appreciation of the finding of microorganisms in this disease.

CHAPTER V

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Diagnosis

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Paul B. Hoeber, 67–69 East 59th, Street, New York.

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